

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 June 2006 (08.06.2006)

PCT

(10) International Publication Number
WO 2006/058411 A1

(51) International Patent Classification:

A61K 31/675 (2006.01) A61K 31/496 (2006.01)
A61P 9/10 (2006.01) A61K 31/4406 (2006.01)
A61K 31/4415 (2006.01) A61K 31/277 (2006.01)
A61K 31/44 (2006.01) A61K 31/138 (2006.01)
A61K 31/34 (2006.01)

(21) International Application Number:

PCT/CA2005/001470

(22) International Filing Date:

26 September 2005 (26.09.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/612,703 24 September 2004 (24.09.2004) US

(71) Applicant (for all designated States except US): **MEDICURE INTERNATIONAL INC.** [CA/CA]; 4 - 1200 Waverley Street, Winnipeg, Manitoba R3T 0P4 (CA).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **FRIESEN, Albert** [CA/CA]; 77 Shorecrest Drive, Winnipeg, Manitoba R3P 1P4 (CA).

(74) Agent: **RIDOUT & MAYBEE LLP**; One Queen Street East, Suite 2400, Toronto, Ontario M5C 3B1 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRIDOXAL-5'-PHOSPHATE AND RELATED COMPOUNDS IN COMBINATION WITH THERAPEUTIC CARDIOVASCULAR COMPOUNDS FOR TREATING ANGINA.

(57) Abstract: Methods for treating angina are described. A method for treating angina is directed to concurrently administering a compound with a therapeutic cardiovascular compound. The combination therapy described employs suitable therapeutic cardiovascular compounds, such as an a calcium channel blocker, a β -adrenergic blocker, nitrates, partial fatty acid oxidation inhibitors, potassium channel activators, or a mixture thereof, in combination with a compound such as pyridoxal-5'-phosphate, pyridoxic acid, pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues, a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof. The invention also includes a novel composition comprising at least one compound and nitrates, partial fatty acid oxidation inhibitors, potassium channel activators, calcium channel blockers, β -adrenergic blockers, or a mixture thereof.



WO 2006/058411 A1

COMPOSITIONS AND METHODS OF TREATING ANGINA

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to US application Serial No. 60/612,703 filed on September 24, 2004.

BACKGROUND

It is estimated that 6,600,000 people in the United States suffer from angina, and an estimated 400,000 new cases of stable angina occur each year. (Framingham Heart Study, National Heart, Lung, and Blood Institute).

The angina therapeutics β -adrenergic-blocking agents and calcium channel blockers are widely used. New classes of drugs are currently being experimentally administered in the treatment of angina. These new drugs include partial fatty acid oxidation inhibitors (pFOX) and potassium channel activators. Depending on the severity, heart disease patients with stable angina may also be treated with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, antiplatelet therapy, diuretics, statins, or mixtures thereof.

These agents have not generally been shown to be effective for acute uses such as the management of an angina attack. Once an attack has commenced, the treatment of choice is normally nitroglycerin. Therefore, to avoid attacks, one treatment course for individuals subject to angina involves the daily administration of a prophylactic dosage of a β -adrenergic-blocking agent such as propranolol.

Although this has been shown effective in reducing the frequency of angina attacks in humans, it has the drawback of virtually constant drug therapy. Some patients do exhibit adverse reactions to β -adrenergic-blocking agents. In particular, at the high dosage levels utilized for prevention of angina, side effects such as bradycardia, hypotension and dizziness can be encountered. Furthermore, patients who are pregnant, suffer hepatic impairment or have bronchitis or emphysema can only undergo the constant drug exposure under closely monitored conditions, if at all. Therefore, there remains a need for other methods of treating patients suffering from angina.

SUMMARY OF THE INVENTION

The invention includes a method of treating angina in a mammal by concurrently administering to the mammal a therapeutically effective amount of a combination of a compound suitable for use in methods of the invention and a therapeutic angina compound. More specifically, the invention includes administering a therapeutically effective amount of at least one of pyridoxal-5'-phosphate, pyridoxic acid, pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues, pharmaceutically acceptable salts thereof, or pharmaceutical compositions thereof concurrently with a therapeutically effective amount of at least one of calcium channel blocker, β -adrenergic-blocker, nitrate, partial fatty acid oxidation inhibitor, potassium channel activator, or mixtures thereof.

The invention also includes compositions comprising at least one of pyridoxal-5'-phosphate, pyridoxic acid, pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues, pharmaceutically acceptable salts thereof, or pharmaceutical compositions thereof and a therapeutically effective amount of at least one of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or a mixture thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates glucose oxidation rates in rat hearts treated with saline (control), DCA, and P5P (MC-1).

DESCRIPTION OF THE INVENTION

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5 for example).

All numbers and fractions thereof are presumed to be modified by the term "about."

It is to be understood that "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R)- or (S)-. The present invention is meant to include all such possible diastereomers and enantiomers as well as their racemic and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and A geometric isomers. Likewise all tautomeric forms are intended to be included.

The invention is directed to methods of treating angina in a mammal by concurrently administering a therapeutically effective amount of pyridoxal-5'-phosphate (also referred to herein as either PLP or P5P), pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues, pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof with a therapeutic angina compound.

As used herein, the phrase "treating angina" includes but is not limited to, reducing or relieving the symptoms of an angina attack, reducing the frequency of angina attack, altering the symptoms of an angina attack, delaying the onset of an angina attack, and reducing the duration of angina attack. "Angina" includes angina pectoris, stress-induced angina, stable angina, unstable angina, and Prinzmetal's angina.

Methods of the invention can be utilized to treat angina pectoris, stress induced angina, stable angina, unstable angina, or Prinzmetal's angina

Angina pectoris results when myocardial oxygen demand is increased to levels that cannot be met through increased coronary blood flow. It usually results because of stenotic atherosclerotic lesions in one or more of the epicardial coronary vessels. Accordingly, angina is typically brought on by physical exertion or emotional stress. Most patients with stable angina can identify specific activities or situations that will predictably elicit the discomfort; walking up an incline or hurrying are common examples. Some variability in the effort threshold is not

uncommon. Activity done in cold weather, after meals or early in the morning may also be more likely to evoke angina. Some patients report that activity with their arms above their heads is more likely to produce the discomfort. The variable effort threshold for angina in some patients suggests that dynamic alterations in coronary blood flow (eg, because of an intermittent increase in coronary vasomotor tone) contribute to fixed atherosclerotic stenosis in limiting blood flow. Episodes of stable angina usually begin gradually and last about 2 to about 10 minutes. Discomfort is usually relieved promptly by rest or sublingual nitroglycerin.

The symptoms of angina pectoris are typically described as a substernal chest discomfort perceived as a tightness, heaviness, pressure, or a burning sensation. It is characteristically nonfocal, i.e., the patient cannot indicate the location with one finger. The discomfort may radiate to the left shoulder or the arms, or to the neck and jaw. Some patients describe their angina in more atypical terms, such as sharp, a "gas pain", discomfort only in the jaw, teeth, forearms, or back, or discomfort beginning in the epigastric region and radiating up into the chest. Other patients describe it as shortness of breath with no definite discomfort, a symptom called angina-equivalent dyspnea.

Stress-induced angina also occurs in some patients with severe aortic valvular stenosis, left ventricular hypertrophy, or pulmonary arterial hypertension in the absence of significant coronary artery stenoses. In these situations, even normal coronary blood flow may be inadequate to meet the heightened myocardial oxygen demand. Angina may also develop in persons with very dilated left ventricles, particularly when accompanied by reduced diastolic coronary perfusion pressure, as in advanced aortic regurgitation.

Angina pectoris that has recently progressed or spontaneously increased in severity, frequency, or duration--particularly if accompanied by rest pain--is considered unstable angina. Patients with the recent onset of angina, particularly if it occurs at low levels of activity or at rest, are also included in this category. Most unstable angina patients have underlying obstructive coronary disease; the unpredictable onset of symptoms or conversion from a stable to an unstable pattern usually results from atherosclerotic plaque fissuring with superimposed platelet--or fibrin-rich thrombi. An unstable pattern can also be precipitated by extracoronary factors (secondary unstable angina). Severe anemia or carbon monoxide exposure,

for example, limits the capacity of the blood to carry or release oxygen and can result in angina under conditions that a patient with coronary disease might otherwise tolerate well. Uncontrolled systemic arterial hypertension, rapid dysrhythmias, or hypoxemia due to pulmonary disease can also provoke angina pectoris, as can hyperthyroidism.

Prinzmetal's angina is similar in character and location to stable angina and often responds to nitroglycerin. It characteristically occurs at rest, however, without obvious provocation or a preceding increase in heart rate or blood pressure. These features are explained by its underlying mechanism: transient coronary artery spasm. Often, the episodes occur in the early morning. Some patients with Prinzmetal's angina report other vasomotor-related symptoms such as migraine headache or Raynaud's phenomenon. (Textbook of Internal Medicine, Third Edition, pages 316-317 (1997).

A "therapeutic angina compound", as used herein, includes angina therapeutics such as β -adrenergic blocking agents, calcium channel blockers, partial fatty acid oxidation inhibitors, potassium channel activators, and nitrates, but does not include pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxic acid, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphate analogues, or pharmaceutically acceptable salts thereof, even though such compounds have been found to have therapeutic use in the treatment of angina.

As used herein mammals include, but are not limited to humans.

A "therapeutically effective amount" as used herein includes a prophylactic amount, for example, an amount effective for preventing the occurrence of an angina attack. For example, a therapeutically effective amount includes an amount suitable for reducing or relieving the symptoms of an angina attack. Moreover, a therapeutically effective amount includes an amount suitable for decreasing the frequency of occurrence of angina attacks. A therapeutically effective amount also includes an amount suitable to alter the symptoms of an angina attack. A therapeutically effective amount also includes an amount suitable to delay the onset of an angina attack. An amount effective to reduce the duration of an angina attack can also be considered a therapeutically effective amount.

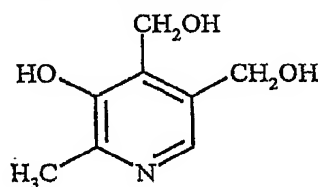
A therapeutic compound can be administered, for example, after an angina attack has occurred. In an alternative embodiment, a composition of the invention can be administered before or during the occurrence of an angina attack.

Therapeutic Compounds Suitable for Use in Methods of the Invention

Methods of the invention include administration of a therapeutically effective amount of a compound including any one or more of pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues, pharmaceutically acceptable salts thereof, or pharmaceutical compositions thereof.

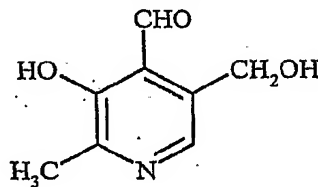
In one embodiment, a therapeutic compound includes any one or more of pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxamine, or a pharmaceutically acceptable salt thereof.

Pyridoxal-5'-phosphate (also referred to as PLP, and P5P), an end product of vitamin B₆ metabolism, plays a vital role in mammalian health. Vitamin B₆ typically refers to pyridoxine, which is chemically known as 2-methyl-3-hydroxy-4,5-di(hydroxymethyl)pyridine and is represented by formula I:



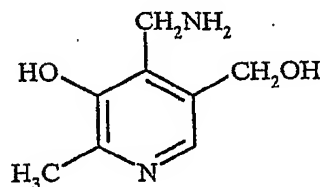
(I)

Yet two additional compounds, pyridoxal (formula II)



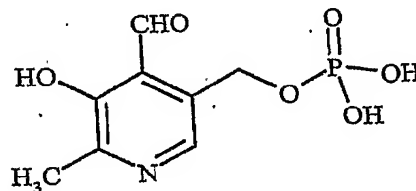
(II)

and pyridoxamine (formula III)



(III),

are also referred to as vitamin B₆. All three compounds serve as precursors to pyridoxal-5'-phosphate (PLP), which is chemically known as 3-hydroxy-2-methyl-5-[(phosphonoxy) methyl]-4-pyridine-carboxaldehyde and is represented by formula IV:



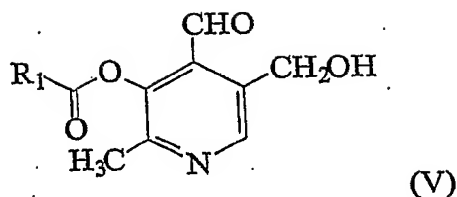
(IV)

PLP is a metabolite of vitamin B₆ inside cells and in blood plasma. Mammals cannot synthesize PLP *de novo* and must rely on dietary sources of precursors such as pyridoxine, pyridoxal, and pyridoxamine, which are metabolized to PLP. For instance, mammals produce PLP by phosphorylating pyridoxine by action of pyridoxal kinase and then oxidizing the phosphorylated product.

PLP is a regulator of biological processes and a cofactor in more than 100 enzymatic reactions. It has been shown to be an antagonist of a purinergic receptor, thereby affecting ATP binding; it has been implicated in modulation of platelet aggregation; it is an inhibitor of certain phosphatase enzymes; and it has been implicated in the control of gene transcription. PLP is also a coenzyme in certain enzyme-catalyzed processes, for example, in glycogenolysis at the glycogen phosphorylase level, in the malate aspartate shuttle involving glycolysis and glycogenolysis at the transamination level, and in homocysteine metabolism. In previous patents (US 6,051,587 and US 6,043,259 which are incorporated by reference herein) the role of pyridoxal-5'-phosphate, and its precursors pyridoxal and pyridoxine (vitamin B₆), in mediating cardiovascular health and in treating cardiovascular related diseases has been disclosed.

Therapeutic compounds include esters of pyridoxic acid and pyridoxic acid 4,5-lactone.

Therapeutic compounds also include any one or more of the 3-acylated analogues of pyridoxal represented by formula V:



where

R_1 is alkyl, or alkenyl, in which alkyl or alkenyl can be interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkanoyloxyaryl, alkoxyalkanoyl, alkoxycarbonyl; or R_1 is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoyloxy; or R_1 is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

or a pharmaceutically acceptable salt thereof.

The term "alkyl" includes a straight or branched saturated aliphatic hydrocarbon radicals, such as, for example, methyl, ethyl, propyl, isopropyl (1-

methylethyl), , butyl, *tert*-butyl (1,1-dimethylethyl), and the like.

The term "alkenyl" includes an unsaturated aliphatic hydrocarbon chain having from 2 to 8 carbon atoms, such as, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-methyl-1-propenyl, and the like.

The above alkyl or alkenyl can optionally be interrupted in the chain by a heteroatom, such as, for example, a nitrogen, sulfur, or oxygen atom, forming an alkylaminoalkyl, alkylthioalkyl, or alkoxyalkyl, for example, methylaminoethyl, ethylthiopropyl, methoxymethyl, and the like.

The above alkyl or alkenyl can optionally be substituted at the terminal carbon by hydroxy, alkoxy, alkanoyloxyaryl, alkanoyloxy, alkoxyalkanoyl, alkoxycarbonyl, or dialkylcarbamoyloxy.

The term "alkoxy" (i.e. alkyl-O-) includes alkyl as defined above joined to an oxygen atom having preferably from 1 to 4 carbon atoms in a straight or branched chain, such as, for example, methoxy, ethoxy, propoxy, isopropoxy (1-methylethoxy), butoxy, *tert*-butoxy (1,1-dimethylethoxy), and the like.

The term "dialkylamino" includes two alkyl groups as defined above joined to a nitrogen atom, in which alkyl has preferably 1 to 4 carbon atoms, such as, for example, dimethylamino, diethylamino, methylethylamino, methylpropylamino, diethylamino, and the like.

The term "alkanoyloxy" includes a group of the formula $(\text{Alk}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-)$. Examples of alkanoyloxy include methanoyloxy, ethanoyloxy, propanoyloxy, and the like. Examples of alkyl substituted at the terminal carbon by alkanoyloxy include 1-ethanoyloxy-1-methylethyl, propanoyloxy-1-methylethyl, and the like.

The term "alkanoyloxyaryl" includes a group of the formula $(\text{Alk}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{Ar}-)$. Examples of alkanoyloxyaryl include methanoyloxyphenyl, ethanoyloxyphenyl, propanoyloxyphenyl, and the like.

The term "aryl" refers to unsaturated aromatic carbocyclic radicals having a single ring, such as phenyl, or multiple condensed rings, such as naphthyl or anthryl. The term "aryl" also includes substituted aryl comprising aryl substituted on a ring by, for example, C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, hydroxy, phenyl, nitro, halo, carboxyalkyl or alkanoyloxy. Aryl groups include, for example, phenyl, naphthyl, anthryl, biphenyl, methoxyphenyl, halophenyl, and the like.

The term "aryloxy" (i.e. aryl-O-) includes aryl having an oxygen atom bonded to an aromatic ring, such as, for example, phenoxy and naphthoxy.

The term "arylthio" (i.e. aryl-S-) includes aryl having a sulfur atom bonded to an aromatic ring, such as, for example, phenylthio and naphthylthio..

The term "aralkyl" refers to an aryl radical defined as above substituted with an alkyl radical as defined above (e.g. aryl-alkyl-). Aralkyl groups include, for example, phenethyl, benzyl, and naphthylmethyl..

Aryl from any of aryl, aryloxy, arylthio, aralkyl, and alkanoyloxyaryl can be unsubstituted or can be substituted on a ring by, for example, C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, hydroxy, nitro, halo, or alkanoyloxy. Examples of substituted aryl include toluyl, methoxyphenyl, ethylphenyl, and the like.

The term "alkoxyalkanoyl" includes a group of the formula

$(\text{Alk}-\text{O}-\text{Alk}-\overset{\text{O}}{\parallel}{\text{C}}-)$. Examples of alkoxyalkanoyl include (2-acetoxy-2-methyl)propanyl, 3-ethoxy-3-propanoyl, 3-methoxy-2-propanoyl, and the like.

The term "alkoxycarbonyl" includes a group of the formula

$(\text{Alk}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-)$. Examples of alkoxy carbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and the like.

The term "dialkylcarbamoyloxy" includes a group of the formula

$(\overset{\text{Alk}}{\text{N}}(\overset{\text{Alk}}{\text{N}})-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-)$. Examples of dialkylcarbamoyloxy include dimethylaminomethanoyloxy, 1-ethyl-1-methylaminomethanoyloxy, and the like. Examples of alkyl substituted at the terminal carbon by alkanoyloxy include dimethylamino-1-methylethyl, 1-ethyl-1-methylaminomethanoyloxy-1-methylethyl, and the like.

The term "halo" includes bromo, chloro, and fluoro.

In the embodiment R_1 includes toluyl, naphthyl, phenyl, phenoxy, dimethylamino, 2,2-dimethylethyl, ethoxy, (2-acetoxy-2-methyl)propanyl, 1-ethanoyloxy-1-methylethyl, *tert*-butyl, acetylsalicyl, and ethanoyloxyphenyl for example.

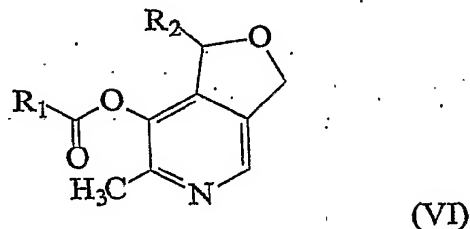
In another embodiment R_1 groups for compounds of formula V are toluyl or naphthyl.

R_1 groups when joined with a carbonyl group form an acyl group $\overset{\text{O}}{\parallel}{\text{R}_1\text{C}}-$ which can include toluoyl or β -naphthoyl for example. Of the toluoyl group, the *p*-isomer is the substituent in one embodiment.

Examples of 3-acylated analogues of pyridoxal include, but are not limited to, 2-methyl-3-toluoyloxy-4-formyl-5-hydroxymethylpyridine and 2-methyl- β -naphthoyloxy-4-formyl-5-hydroxymethylpyridine.

Examples of compounds of formula V and methods of synthesizing those compounds are described in U.S. Patent No. 6,339,085, the disclosure of which is incorporated herein by reference.

Therapeutic compounds also include any one or more of the 3-acylated analogues of pyridoxal-4,5-aminal represented by formula VI:



where

R₁ is alkyl, or alkenyl, in which alkyl or alkenyl can be interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkanoyloxyaryl, alkoxyalkanoyl, alkoxycarbonyl, or dialkylcarbamoyloxy; R₁ is alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxycarbonyl; dialkylcarbamoyloxy; R₁ is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

R₂ is a secondary amino group;

or a pharmaceutically acceptable salt thereof.

The terms "alkyl," "alkenyl," "alkoxy," "dialkylamino," "alkanoyloxy," "alkanoyloxyaryl," "alkoxyalkanoyl," "alkoxycarbonyl," "dialkylcarbamoyloxy," "halo," "aryl," "aryloxy," "arylthio," and "aralkyl" are as defined above for formula V.

The term "secondary amino" group includes a group of formula VII:



derived from a secondary amine R₃R₄NH, in which R₃ and R₄ are each independently alkyl, alkenyl, cycloalkyl, aryl, or, when R₃ and R₄ are taken together, may form a ring with the nitrogen atom and which may be interrupted by a heteroatom, such as, for example, a nitrogen, sulfur, or oxygen atom. The terms "alkyl," "alkenyl," and "aryl" are used as defined above in forming secondary amino

groups such as, for example, dimethylamino, methylethylamino, diethylamino, dialkylamino, phenylmethylamino, diphenylamino, and the like.

The term "cycloalkyl" refers to a saturated hydrocarbon having from 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms, such as, for example, cyclopropyl, cyclopentyl, cyclohexyl, and the like.

When R₃ and R₄ are taken together to form a ring with the nitrogen atom, a cyclic secondary amino group, such as, for example, piperidino, can be formed. When the cyclic secondary amino group is interrupted with a heteroatom, a group such as, for example, piperazino or morpholino can be formed.

In one embodiment R₁ groups include toluyl, naphthyl, phenyl, phenoxy, dimethylamino, 2,2-dimethylethyl, ethoxy, (2-acetoxy-2-methyl)propanyl, 1-ethanoxyloxy-1-methylethyl, *tert*-butyl, acetylsalicyl, and ethanoxyloxyphenyl for example.

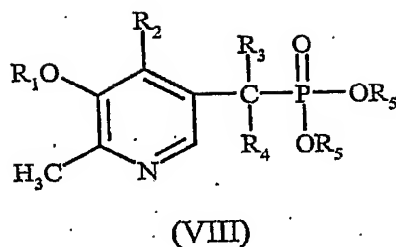
In another embodiment R₁ groups can include toluyl, e.g., *p*-toluyl, naphthyl, *tert*-butyl, dimethylamino, acetylphenyl, hydroxyphenyl, or alkoxy, e.g., methoxy.

Such R₁ groups when joined with a carbonyl group form an acyl group $\text{R}_1\text{C}(=\text{O})-$ which can include toluoyl, β -naphthoyl, pivaloyl, dimethylcarbamoyl, acetylsalicyloyl, salicyloyl, or alkoxycarbonyl. In another embodiment, R₂, the secondary amino group can be morpholino.

Examples of 3-acylated analogues of pyridoxal-4,5-aminal include, but are not limited to, 1-morpholino-1,3-dihydro-7-(*p*-toluoyloxy)-6-methylfuro(3,4-*c*)pyridine; 1-morpholino-1,3-dihydro-7-(β -naphthoyloxy)-6-methylfuro(3,4-*c*)pyridine; 1-morpholino-1,3-dihydro-7-pivaloyloxy-6-methylfuro(3,4-*c*)pyridine; 1-morpholino-1,3-dihydro-7-carbamoyloxy-6-methylfuro(3,4-*c*)pyridine; and 1-morpholino-1,3-dihydro-7-acetylsalicyloxy-6-methylfuro(3,4-*c*)pyridine.

Examples of compounds of formula VI and methods of synthesizing those compounds are described in U.S. Patent No. 6,339,085, the disclosure of which is incorporated herein by reference.

Therapeutic compounds include any one or more pyridoxal phosphonate analogues represented by the formula VIII:



where

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$, $-\text{CO}_2\text{R}_6$ in which R_6 is hydrogen, alkyl, or aryl; or R_2 is $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 ;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino or arylamino; or

R_3 and R_4 are halo; and

R_5 is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2\text{R}_7$ in which R_7 is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable salt thereof.

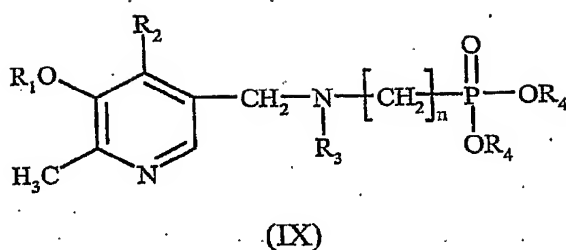
The terms "alkyl," "alkoxy," "alkanoyloxy," "halo," "aryl," and "aralkyl" are as defined above for formula V.

The term "alkylamino" refers to $-\text{NH-alkyl}$ with alkyl as defined above. Alkylamino groups include those with 1-6 carbons in a straight or branched chain, such as, for example, methylamino, ethylamino, propylamino, and the like.

The term "arylamino" refers to $-\text{N-aryl}$ with aryl as defined above. Arylamino includes $-\text{NH-phenyl}$, $-\text{NH-biphenyl}$, $-\text{NH-4-methoxyphenyl}$, and the like.

Examples of compounds of formula VIII include those where R_1 is hydrogen, or those where R_2 is $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 , or those where R_3 is hydrogen and R_4 is F, MeO- or $\text{CH}_3\text{C(O)O-}$, or those where R_5 is alkyl or aralkyl. Additional examples of compounds of formula VIII include those where R_3 and R_4 are F, or those where R_5 is t-butyl or benzyl.

Therapeutic compounds further include any one or more pyridoxal phosphonate analogues represented by the formula IX:



in which

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$ or $-\text{CO}_2\text{R}_5$ in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 ;

R_3 is hydrogen, alkyl, aryl, or aralkyl;

R_4 is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2\text{R}_6$ in which R_6 is hydrogen, alkyl, aryl, or aralkyl;

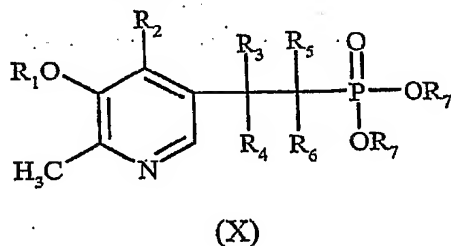
n is 1 to 6;

or a pharmaceutically acceptable salt thereof.

The terms "alkyl," "aryl," and "aralkyl" are as defined above for formula V.

Examples of compounds of formula IX include those where R_1 is hydrogen, or those where R_2 is $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 , or those where R_3 is hydrogen; or those where R_4 is alkyl or hydrogen. Additional examples of compounds of formula IX include those where R_4 is ethyl.

Therapeutic compounds further include any one or more pyridoxal phosphonate analogues represented by the formula X:



in which

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$ or $-\text{CO}_2\text{R}_8$ in which R_8 is hydrogen, alkyl, or aryl; or

R₂ is -CH₂O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁;

R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy or alkanoyloxy; or

R₃ and R₄ can be taken together to form =O;

R₅ and R₆ are hydrogen; or

R₅ and R₆ are halo;

R₇ is hydrogen, alkyl, aryl, aralkyl, or -CO₂R₈ in which R₈ is

hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable salt thereof.

The terms "alkyl," "alkoxy," "alkanoyloxy," "halo," "aryl," and "aralkyl" are as defined above for formula VI.

Examples of compounds of formula IX include those where R₁ is hydrogen, or those where R₂ is -CH₂OH, or -CH₂O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁, or those where R₃ and R₄ taken together form =O, or those where R₅ and R₆ are F, or those where R₇ is alkyl.

Additional examples of compounds of formula IX include those where R₄ is OH or CH₃C(O)O-, those where R₇ is ethyl.

Pharmaceutically acceptable salts of the compounds of formulas I, II, III, IV, V, VI, VII, IX, or X include acid addition salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorus, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, n-methyl glutamine, etc. (see, e.g., Berge et al., *J. Pharmaceutical Science*, 66: 1-19 (1977)).

The salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of a desired acid to produce the salt in the conventional manner. The free base form can be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable salts of the compounds of formulas VIII, IX, and X include metals such as alkali and alkaline earth metals. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Also included are heavy metal salts such as for example silver, zinc, cobalt, and cerium.

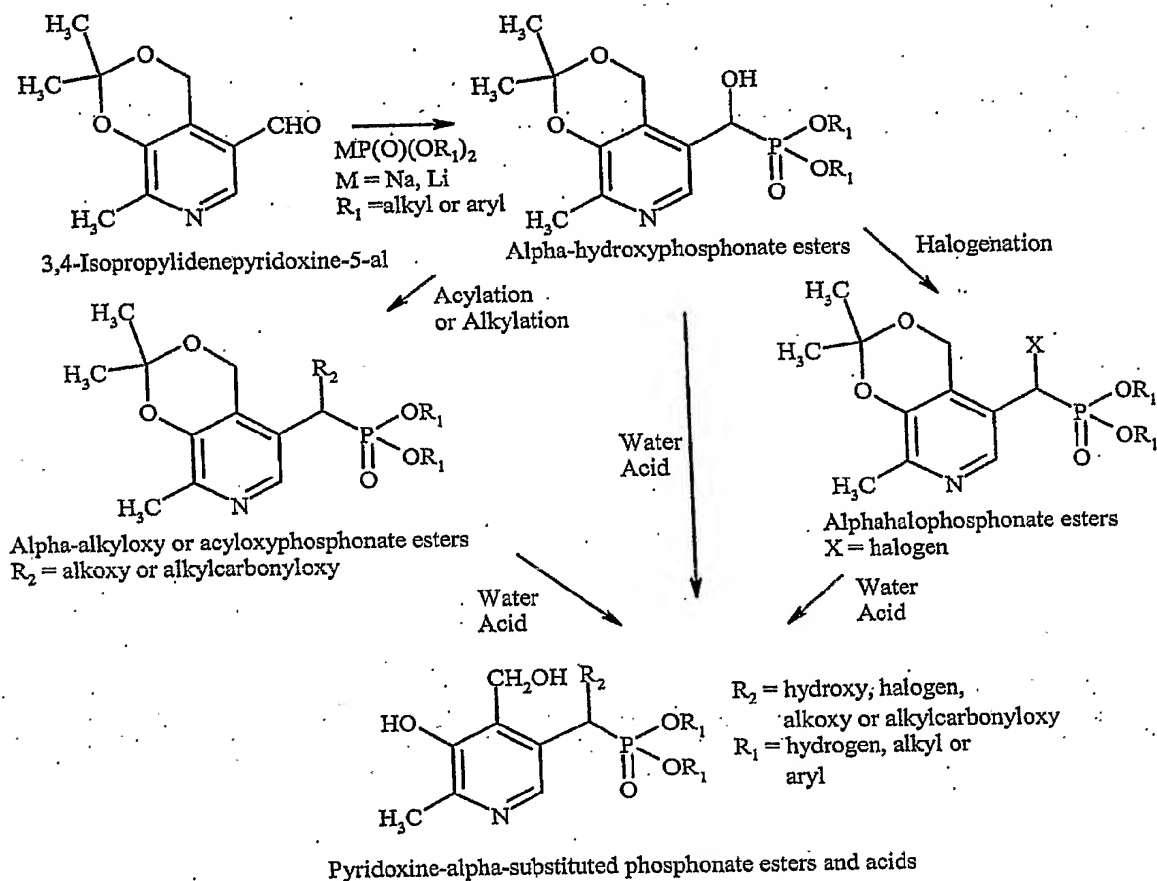
Any of the above compounds may be mixed with a nitrate, partial fatty acid oxidation inhibitor, potassium channel activator, or mixtures thereof, to form a single novel composition.

Syntheses

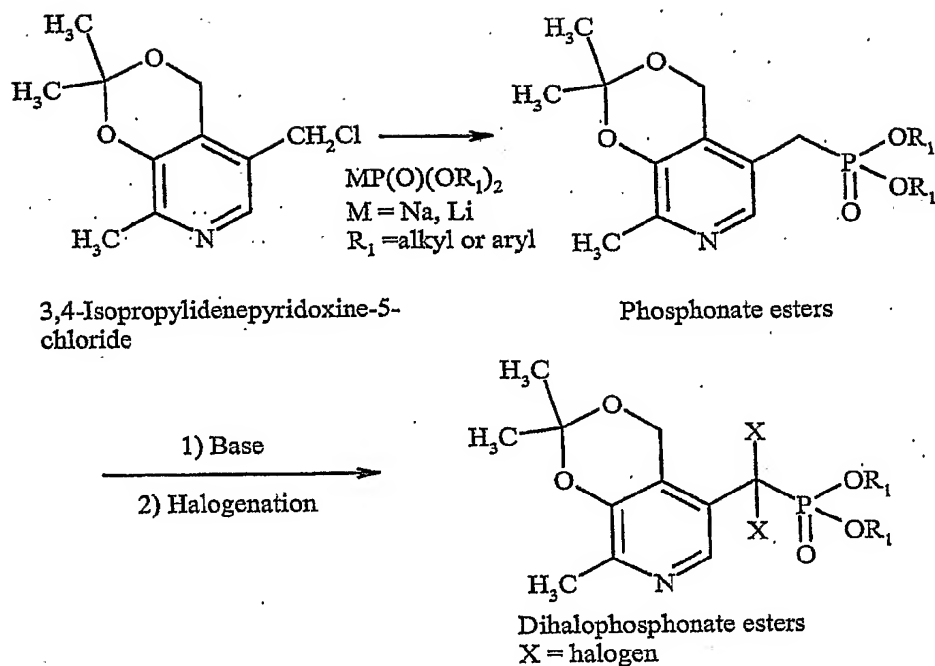
To prepare a compound of formula VIII, 3,4-isopropylidenepyridoxine-5-al can be treated with a phosphonating agent, such as, a metal salt of di-tert-butyl phosphite or dibenzyl phosphite or diphenyl phosphite, to give protected alpha-hydroxyphosphonates. The protected alpha-hydroxyphosphonates can be treated with an acylating agent in an aprotic solvent, such as acetic anhydride in pyridine, or with an alkylating agent, such as methyl iodide and sodium hydride in tetrahydrofuran (THF), to give alpha-alkylcarbonyloxy or alpha-alkyloxyphosphonates esters respectively.

Alternatively the protected alpha-hydroxyphosphonates can be treated with an agent to convert the hydroxyl group to a halogen, such as conversion to a fluoro group with DAST (diethylaminosulfurtrifluoride), to prepare the alpha-halophosphonate esters. The isopropylidene protecting group is removed from the fully protected alpha-substituted phosphonates by reacting them with water and an acid, such as 20% water in acetic acid, to prepare the pyridoxine-alpha-substituted phosphonate esters. The ester groups can be removed from the phosphonate groups of the pyridoxine-alpha-substituted phosphonate esters by further treating them with

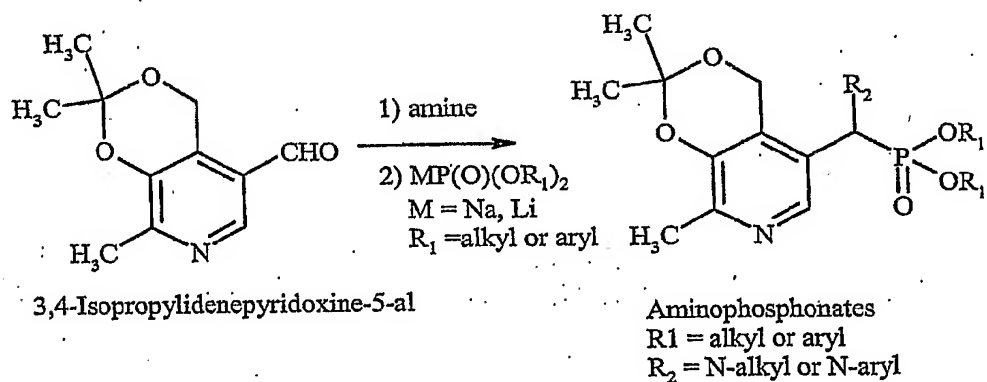
acid in water, such as 20% water in acetic acid, to give the corresponding phosphonic acids as can be seen in the following scheme.



Alternatively, to prepare a compound of formula I, 3,4-isopropylidenepyridoxine-5-halide can be treated with a phosphonating agent, such as, a metal salt of di-tert-butyl phosphite or dibenzyl phosphite or diphenyl phosphite, to give protected phosphonates. The protected phosphonates are treated with a base, such as sodium hexamethyldisilazane (NaHMDS), and a halogenating agent, such as N-fluorobenzenesulfonimide (NFSi), to provide the dihalophosphonates as can be seen in the following scheme.

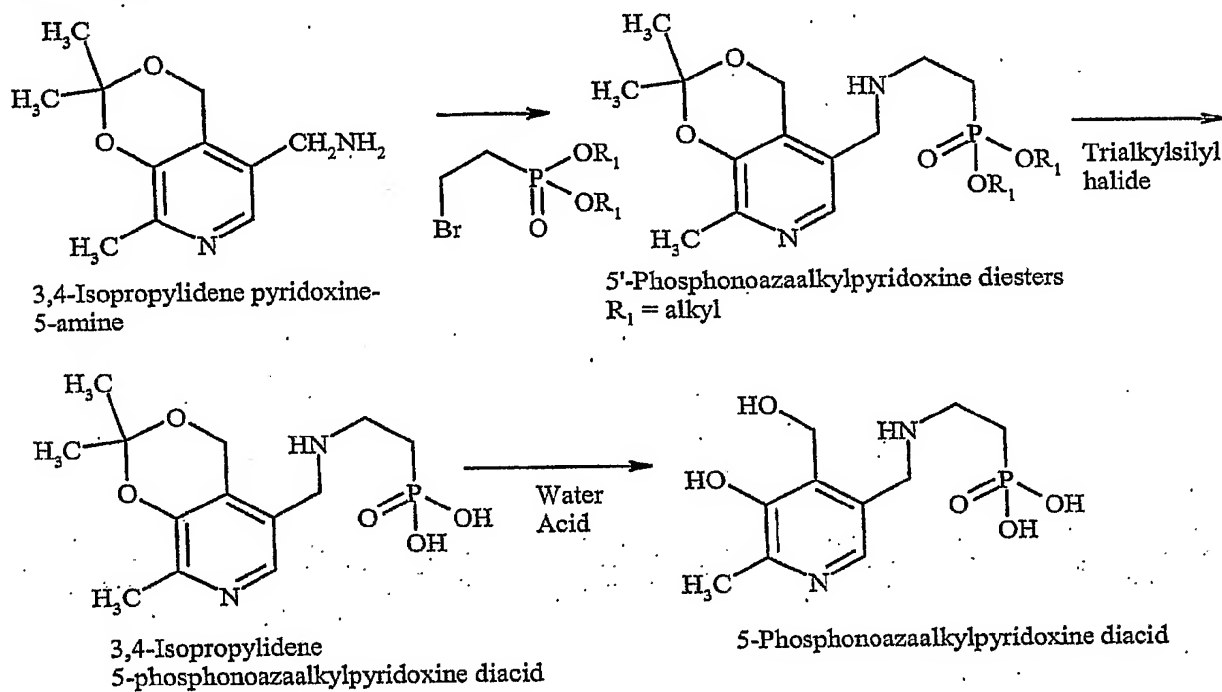


Alternatively, to prepare a compound of formula VIII, 3,4-isopropylidenepyridoxine-5-al can be treated with an amine, such as p-methoxyaniline or p-aminobiphenyl, and a phosphonating agent, such as, a metal salt of di-tert-butyl phosphite, dibenzyl phosphite or diphenyl phosphite, to give protected aminophosphonates as can be seen in the following scheme.

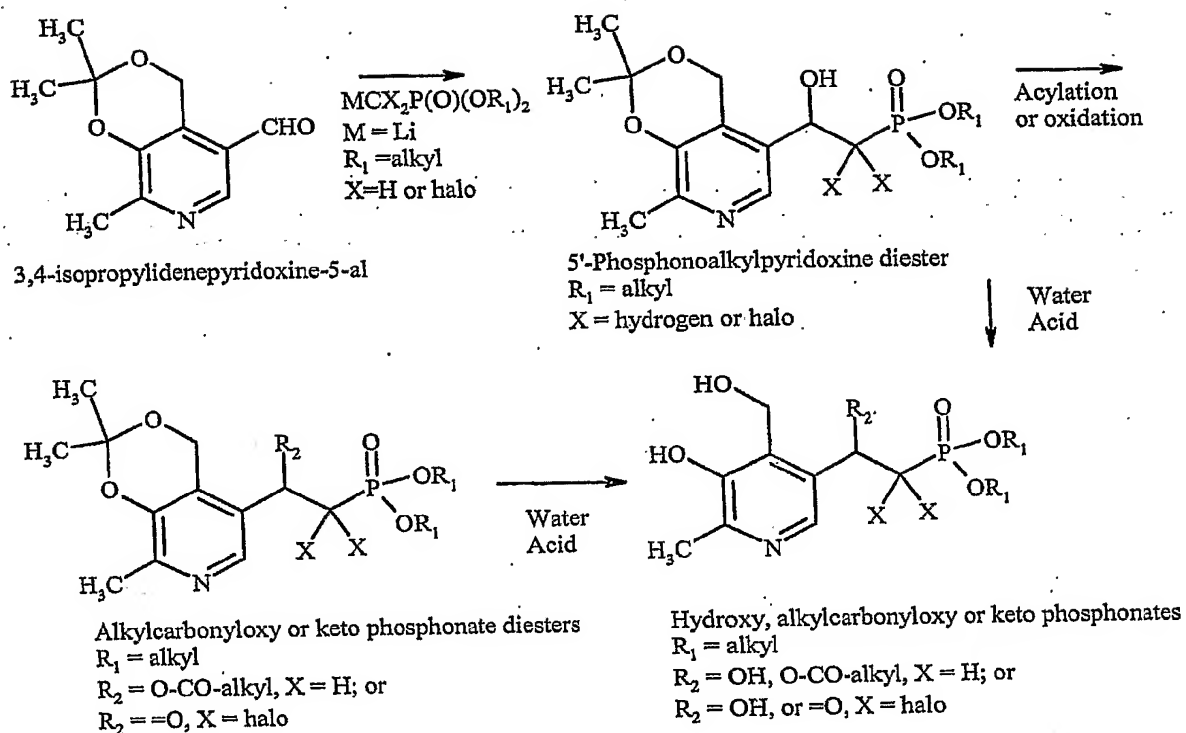


To prepare a compound of formula IX, 3,4-isopropylidenepyridoxine-5-amine can be used as a starting material. The amine is treated with a haloalkylphosphonate diester, such as diethyl bromomethylphosphonate, to give 5'-phosphonoazaalkylpyridine diesters. Reaction of the 3,4-isopropylidene-5'-phosphonoazaalkylpyridoxine diesters with a trialkylsilyl halide, such as trimethylsilyl bromide, in an aprotic solvent, such as acetonitrile, removes the ester

groups of the phosphonate diester to provide the corresponding free 3,4-isopropylidene-5'-phosphonoazaalkylpyridoxine diacid. The acetonide protecting group on the 3 and 4 position of the pyridoxine ring on the 3,4-isopropylidene-5'-phosphonoazaalkylpyridoxine diacid can be removed by reaction with acid and water, such as 20% water in acetic acid as can be seen in the following scheme.



To prepare a compound of formula X, 3,4-isopropylidenepyridoxine-5-al can be reacted with a metal salt of a methyl, or dihalomethyl, phosphonate diester to produce 5'-phosphonoalkylpyridoxine diesters. The 5'-hydroxyl group of this product is acylated by an acylating agent, such as acetic anhydride in pyridine, to provide the corresponding O-acyl derivatives respectively, or oxidized to the keto functional group by an oxidizing agent, such as manganese dioxide. The blocking group at the 3 and 4 positions and the phosphonate ester groups of the hydroxy, alkylcarbonyloxy and keto phosphonate diesters are hydrolyzed by reaction with acid and water, such as 20% water in acetic acid, to provide the corresponding phosphonate diesters, without the blocking group at the 3 and 4 position. These reactions are illustrated in the following scheme.



Pharmaceutical Composition Suitable for Use with Methods of the Invention

A therapeutic compound as defined above can be formulated into a pharmaceutical composition for use in methods of the invention. A pharmaceutical composition is suitable for treating angina.

A pharmaceutical composition comprises a pharmaceutically acceptable carrier, at least one therapeutic compound of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof, and at least one of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic-blocker, a potassium channel activator, or a mixture thereof. A pharmaceutically acceptable carrier includes, but is not limited to, physiological saline, ringers, phosphate-buffered saline, and other carriers known in the art. Pharmaceutical compositions can also include additives, for example, stabilizers, antioxidants, colorants, excipients, binders, thickeners, dispersing agents, reabsorption enhancers, buffers, surfactants, preservatives, emulsifiers, isotonicizing agents, and diluents. Pharmaceutically acceptable carriers and additives can be chosen such that side effects from the pharmaceutical compound are minimized and

the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

Methods of preparing pharmaceutical compositions containing a pharmaceutically acceptable carrier, at least one therapeutic compound of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof are known to those of skill in the art, and at least one of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic-blocker, a potassium channel activator, or a mixture thereof.

All methods can include the step of bringing the compound of the invention in association with the carrier and additives. The formulations generally are prepared by uniformly and intimately bringing the compound of the invention into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired unit dosage form.

Generally, a solution of a therapeutic compound, for example PLP, may be prepared by simply mixing PLP with a pharmaceutically acceptable solution, for example, buffered aqueous saline solution at a neutral or alkaline pH (because PLP is essentially insoluble in water, alcohol, and ether), at a temperature of at least room temperature and under sterile conditions. In one embodiment, the PLP solution is prepared immediately prior to administration to the mammal. However, if the PLP solution is prepared at a time more than immediately prior to the administration to the mammal, the prepared solution can be stored under sterile, refrigerated conditions. Furthermore, because PLP is light sensitive, the PLP solution can be stored in containers suitable for protecting the PLP solution from the light, such as amber-colored vials or bottles.

A pharmaceutical composition or therapeutic compound can be administered enterally or parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. Compounds and compositions of the invention can also be administered nasally, sub-lingually, and in suppository form. When administered, the pharmaceutical composition or therapeutic compound should be at or near body temperature.

Methods of Treatment

A physician of ordinary skill can readily determine a subject who may be suffering or is likely to suffer from angina. Regardless of the route of administration selected, the therapeutic compounds of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof can be formulated into pharmaceutically acceptable unit dosage forms by conventional methods known to the pharmaceutical art. An effective but nontoxic quantity of the compound can be employed in treatment.

The therapeutic compound of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof can be administered in enteral unit dosage forms, such as, for example, tablets, sustained-release tablets, enteric coated tablets, capsules, sustained-release capsules, enteric coated capsules, pills, powders, granules, solutions, and the like. They can also be administered parenterally, such as, for example, subcutaneously, intramuscularly, intradermally, intramammarily, intravenously, and other administrative methods known in the art. They can further be administered nasally, sub-lingually, or in suppository form.

Although it is possible for a therapeutic compound of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof as described above to be administered alone in a unit dosage form, preferably the compound is administered in admixture as a pharmaceutical composition.

The ordinarily skilled physician will readily determine and prescribe a therapeutically effective amount of at least one therapeutic compound of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof to treat angina. In so proceeding, the physician could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained. Typically, the particular type of angina, the severity of the symptoms, or the frequency of the attacks, the compound to be administered, the route of administration, and the characteristics of the mammal to be treated, for example, age, sex, and weight, can be considered in determining the effective amount to administer. In one embodiment of the invention, a therapeutic amount is in a range of about 0.1-100 mg/kg of a patient's body weight, in another embodiment, in the range of about 0.5-50 mg/kg of a patient's body weight, per daily dose. The compound can be administered for periods of short or long duration. Although some individual

situations can warrant to the contrary, short-term administration, for example, 30 days or less, of doses larger than 25 mg/kg of a patient's body weight is chosen when compared to long-term administration. When long-term administration, for example, months or years, is utilized, the suggested dose generally should not exceed 25 mg/kg of a patient's body weight.

A therapeutically effective amount of a therapeutic compound of formula I, II, III, IV, V, VI, VII, IX, or X or a pharmaceutically acceptable salt thereof for treating angina can be administered prior to, concurrently with, or after the onset of an angina attack.

A therapeutic compound of the invention can be administered concurrently with or subsequent to compounds that are already known to be suitable for treating angina. "Concurrent administration" and "concurrently administering" as used herein includes administering a therapeutic compound and a known therapy in admixture such as, for example, in a pharmaceutical composition or in solution, or as separate components, such as, for example, separate pharmaceutical compositions or solutions administered consecutively, simultaneously, or at different times but not so distant in time such that the therapeutic compound and the known therapy cannot interact and a lower dosage amount of the active ingredient cannot be administered.

Methods of the invention include concurrently administering pyridoxal-5'-phosphate, pyridoxic acid, pyridoxal, pyridoxine, pyridoxamine, 3-acylated analogues of pyridoxal, 3-acylated analogues of pyridoxal-4,5-aminal, pyridoxine phosphonate analogues with a therapeutic angina compound to treat angina.

Therapeutic angina compounds that may be concurrently administered with a compound suitable for use in methods of the invention include a calcium channel blocker, a β -adrenergic blocker, nitrates, fatty acid oxidation inhibitors (e.g., ranolazine), potassium channel activators (e.g., nicorandil), and mixtures thereof. Calcium channel blockers include, but are not limited to, verapamil, diltiazem, nifedipine, felodipine, amlodipine, and nisoldipine. β -adrenergic blockers include, but are not limited to, acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, and propranolol. Nitrates include, but are not limited to, nitroglycerine, isosorbide dinitrate, and isosorbide mononitrate.

This invention will be further characterized by the following examples. These examples are not meant to limit the scope of the invention, which has been fully set forth in the foregoing description. Variations within the scope of the invention will be apparent to those skilled in the art.

EXAMPLES

All reagents used in the following Examples can be purchased from Aldrich Chemical Company (Milwaukee, WI or Allentown, PA).

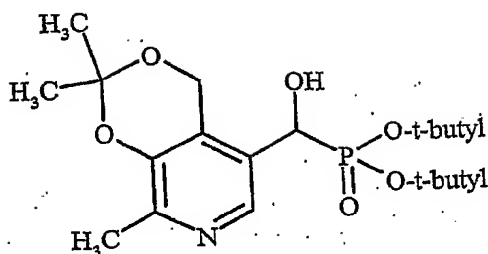
Example 1: Synthesis of di-*t*-butyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)hydroxymethylphosphonate

Di-*t*-butyl phosphite (16.3 g, 84 mmol) was added to a solution of NaH (3.49 g, 60%, 87.2 mmol) in THF (60 mL) under nitrogen at 0°C. The temperature of the resulting solution was raised to room temperature and the solution stirred for 15 min, then cooled to 0°C again. To this solution, (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (11.41 g, 55.05 mmol) in THF (30 mL) was slowly added then the temperature raised to room temperature again and stirring continued for 2 h. The reaction was quenched by adding saturated NaHCO₃ (40 ml), and diluted with diethyl ether (200 mL). The ether layer was separated, washed with saturated aqueous NaHCO₃ (40 ml, 5%), then saturated brine (3 x 20 mL). The ether layer was dried (MgSO₄), filtered and evaporated to give crude product as a colorless solid. This solid was washed with hexane to remove the oil (from the NaH) and unreacted phosphite. The solid was recrystallized from a mixture of diethyl ether : hexane : ethyl acetate (230 mL : 70 mL : 15 mL). The colorless crystal (17.9 g, 81%) were filtered and washed with hexane.

¹H NMR (CDCl₃): 1.42 (9H, d), 1.46 (9H, d), 1.51 (6H, d), 2.38 (3H, s), 4.70 (1H, d), 4.89-5.13 (2H, m), 8.11 (1H, s).

³¹P NMR (H-decoupled, CDCl₃): 13.43 (s).

This structure can be represented by formula:

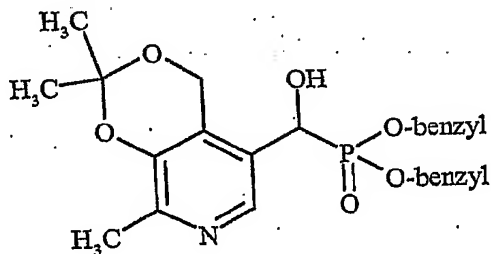


Example 2: Synthesis of dibenzyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)hydroxymethylphosphonate

Dibenzyl phosphite (1.89 g, 9.62 mmol) was mixed with the (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (1.00g, 4.81mmol) and stirred at room temperature for an hour. To this thick syrup was added activated basic alumina (1g). The reaction mixture was then stirred at 80°C for one hour. The reaction mixture was diluted with dichloromethane (50 mL), and filtered through Celite to remove alumina. The dichloromethane solution was washed with saturated, aqueous NaHCO₃ (20 mL), then saturated brine (3 x 10 mL). The dichloromethane layer was dried (MgSO₄), filtered and evaporated to give crude product as a colorless solid. The crude product was purified by silica gel column chromatography, using ether: hexanes (1:2) as eluent to give 1.3 g (58%).

¹H NMR (CDCl₃): 1.30 (3H, s), 1.45 (3H, s), 2.30 (3H, s), 4.86-4.99 (7H, s), 7.18-8.07 (10H, s), 8.08 (1H, s).

This structure can be represented by formula:



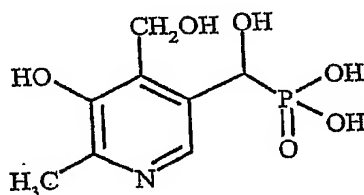
Example 3: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)hydroxymethyl phosphonic Acid

The product of Example 1 above, of formula V, (10 g, 24.9 mmol) was dissolved in acetic acid (80% in water, 100 ml) and heated at 60°C for 1 d. Colorless precipitate was formed, however, the reaction was not complete. Another 50 ml of 80% acetic acid in water was added to the mixture and the mixture stirred at 60°C for another day. The solid was filtered off, washed with cold water, then methanol and dried to give a colorless solid (4.78 g, 77%).

^1H NMR (D_2O): 2.47 (3H, s), 4.75-4.79 (2H, m), 5.15-5.19 (1H, d), 7.82 (1H, s).

^{31}P NMR (H-decoupled D_2O): 14.87 (s).

This structure can be represented by formula:



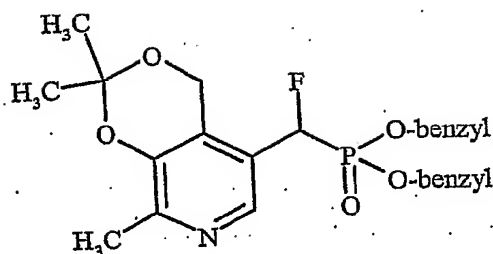
Example 4: Synthesis of dibenzyl (α ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethylphosphonate

The protected alpha-hydroxy phosphonate from Example 2 above of structure VI (1.0 g, 2.49 mmol) was dissolved in dichloromethane (10 mL), and the solution cooled to -78°C. To this solution was added diethylaminosulfurtrifluoride (DAST) (0.8 g, 4.98 mmol). The reaction was stirred at -78°C under nitrogen for 20 minutes then allowed to stand at room temperature overnight. The reaction mixture was diluted with dichloromethane (50 ml), and washed with saturated, aqueous NaHCO_3 (125 mL). The dichloromethane layer was dried (MgSO_4), filtered and evaporated to give crude fluorophosphonate as a yellow solid. The crude product was purified by silica gel column chromatography, using ethyl acetate: hexanes (2:1) as the eluent to give 600 mg (60%).

^1H NMR (CDCl_3): 1.42 (3H, s), 1.52 (3H, s), 2.40 (3H, s), 4.91-4.97 (6H, m), 5.46-5.61 (1H, dd), 7.23-7.34 (10H, m), 8.01 (1H, s).

^{31}P NMR (H-decoupled, F-coupled, CDCl_3): 16.36-16.08 (d).

This structure can be represented by formula:



Example 5: Synthesis of di-t-butyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethylphosphonate

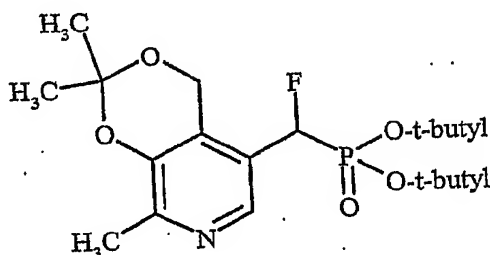
The protected alpha-hydroxy phosphonate from Example 1 of structure V (3 g, 7.55 mmol) was dissolved in dichloromethane (30 mL), and the solution cooled to -78°C . To this solution was added diethylaminosulfurtrifluoride (DAST) (1.22 g, 7.57 mmol). The reaction was stirred at -78°C under nitrogen for 5 minutes, quenched by addition of saturated, aqueous NaHCO_3 (2 mL) then allowed to warm room temperature. The reaction mixture was diluted with dichloromethane (50 mL), and washed with saturated, aqueous NaHCO_3 (2 x 20 mL). The dichloromethane layer was dried (MgSO_4), filtered and evaporated to give crude fluorophosphonate. The crude product was purified by silica gel column chromatography, using ethyl acetate: hexanes (1:1) as the eluent to give 350 mg (12%).

^1H NMR (CDCl_3): 1.44 (9H, s), 1.46 (9H, s), 1.52 (3H, s), 1.56 (3H, s), 2.41 (3H, s), 4.98-5.14 (2H, m), 5.32-5.52 (1H, dd), 8.03 (1H, s).

^{31}P NMR (H-decoupled, F-coupled, CDCl_3): 6.53, 7.24.

^{19}F NMR (H-decoupled, CDCl_3): -202.6, -203.0

This structure can be represented by formula:



Example 6: Synthesis of di-t-butyl (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethyl phosphonate

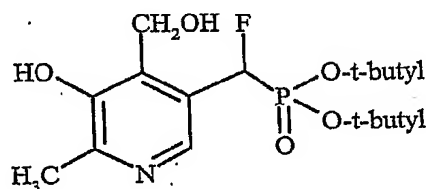
The protected di-*t*-butyl alpha-fluoro phosphonate from Example 5 of structure IX (3.2 g 7.8 mmol) was dissolved in acetic acid (80% in water, 50 ml) and heated at 60°C for 24 hours. The pale yellow solid was filtered off, washed with cold water and methanol, and then dried to give a creamy solid (2.21 g, 70%).

^1H NMR (CDCl_3): 1.41 (9H, s), 1.44 (9H, s), 1.49 (3H, s), 1.51 (3H, s), 2.42 (3H, s), 4.99-5.07 (2H, m), 5.33-5.51 (1H, d,d), 8.04 (1H, s).

^{31}P NMR (H-decoupled, F-Coupled, CDCl_3): 7.10-7.80 (d).

^{19}F NMR (H, P-Coupled, CDCl_3): -203.07 to -202.61 (dd).

This structure can be represented by formula:



Example 7: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)fluoromethyl phosphonic acid

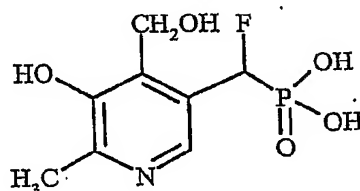
The protected di-*t*-butyl alpha-fluoro phosphonate from Example 5 of structure IX (200 mg, 0.5 mmol) was dissolved in acetic acid (80% in water, 15 ml) and heated at 75°C for 24 hours. The solvent was removed by evaporation on a rotary evaporator using toluene to codistill the water. The crude product (183 mg) was purified by column chromatography on silica using chloroform:methanol:water (65:35:2) as eluent to give 60 mg (55%).

^1H NMR (D_2O): 2.46 (3H, bs), 4.65-4.90 (2H, dd), 5.81-6.01 (1H, dd), 7.74 (1H, bs).

^{31}P NMR (H-decoupled, F-Coupled, CDCl_3): 9.3 (d).

^{19}F NMR (H, P-Coupled, CDCl_3): -197 to -196 (dd).

This structure can be represented by formula:



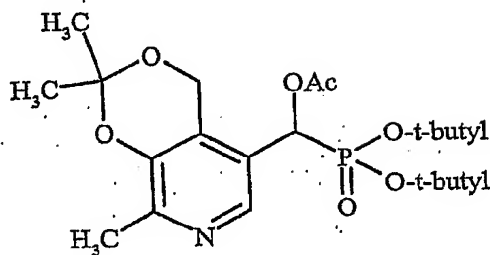
Example 8: Synthesis of di-t-butyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)acetoxymethylphosphonate

The product of Example 1 above, of formula V (1.0 g, 2.49 mmol) was dissolved in dichloromethane (20 mL), the solution cooled to -5°C , and pyridine (2 mL) added, followed by acetic anhydride (1 mL). The reaction temperature was slowly allowed to reach room temperature. After one hour, the reaction was quenched by adding dilute aqueous hydrochloric acid (10%, 75 mL), and then diluted with dichloromethane (25 mL). After separation of the aqueous layer the methylene chloride layer washed with saturated NaHCO_3 (2 x 20 mL). The dichloromethane layer was dried (MgSO_4), filtered and evaporated to give crude alpha acetoxy phosphonate as a colorless solid. The crude product was purified by silica gel column chromatography, using ethyl acetate: hexanes (2:1) as the eluent to give the product in good yield.

^1H NMR (CDCl_3): 1.31 (9H, d), 1.36 (9H, d), 1.49 (6H, d), 2.1 (3H, s), 2.38 (3H, s), 5.04 (2H, d), 5.72-5.76 (1H, d), 8.11 (1H, s).

^{31}P NMR (H-decoupled, CDCl_3): 13.43 (s).

This structure can be represented by formula:



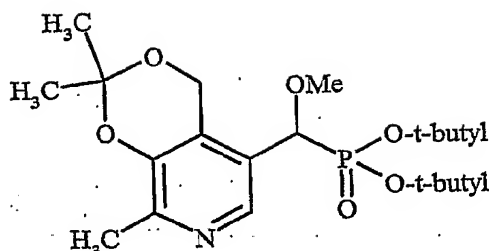
Example 9: Synthesis of di-t-butyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methoxymethylphosphonate

The product of Example 1 above, of formula V (300 mg, 0.75 mmol) was dissolved in 15ml of THF and reaction vessel was purged with N₂ gas. Sodium hydride (21 mg, 0.9 mmol) was added, and the solution stirred for 5 minutes before cooling to 0°C. Methyl iodide (160 mg, 1.1 mmol) was then injected and reaction vessel was gradually allowed to reach room temperature. TLC (ethyl acetate) indicated that the reaction was complete in 3 hours. The solution was diluted with methylene chloride (250 mL), washed with dilute, aqueous HCL (10%, 100 mL), then saturated, aqueous NaHCO₃, dried (MgSO₄) and evaporated. The crude product was chromatographed on silica gel using ethyl acetate/hexanes (1:1) as the eluent to give 132 mg (32%).

¹H NMR (CDCl₃): 1.41 (18H, s), 1.51 (3H, s), 1.54 (3H, s), 2.40 (3H, s), 3.33 (3H, s), 4.20-4.26 (1H, d), 5.05 (2H, bs), 8.01 (1H, s).

³¹P NMR (H-decoupled, CDCl₃): 10.88 (s).

This structure can be represented by formula:

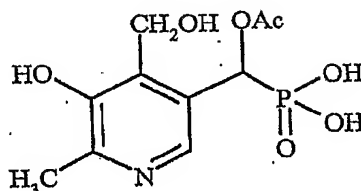


Example 10: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)acetoxymethyl phosphonic Acid

The product of Example 8 above, of formula XII, (50 mg, 0.11 mmol) was added to acetic acid (80% in water) and stirred for 24 hours at 60°C. The solvent was removed by evaporation on a rotary evaporator using toluene to codistill the water. The crude product was purified by chromatography on silica gel column using CH₂Cl₂/MeOH/H₂O (65:35:4) as eluent to give 22.8 mg (76%).

¹H NMR (D₂O): 2.23 (3H, s), 2.51 (3H, s), 4.6 – 5.1 (2H, m), 6.1 (1H, d), 7.85 (1H, s).

This structure can be represented by formula:



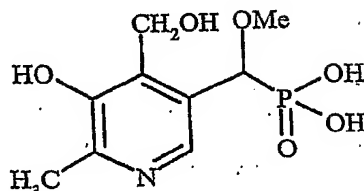
Example 11: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methoxymethyl phosphonic Acid

The product of Example 9 above, of formula XIII (132 mg, 0.32 mmol) was dissolved in acetic acid (80% in water, 25mL) and stirred at 60°C for 24 hours. The solvent was removed by evaporation on a rotary evaporator using toluene to codistill the water. The crude product was purified by chromatography on silica gel column using CH₂Cl₂/MeOH/H₂O (65:35:4) as eluent to give the product in good yield.

¹H NMR (D₂O): 2.52 (3H, s), 3.32 (3H, s), 4.47-4.88 (2H, m), 7.87 (1H, s).

³¹P NMR (H-decoupled, D₂O): 13.31 (s)

This structure can be represented by formula:



Example 12: Synthesis of dibenzyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)difluoromethylphosphonate

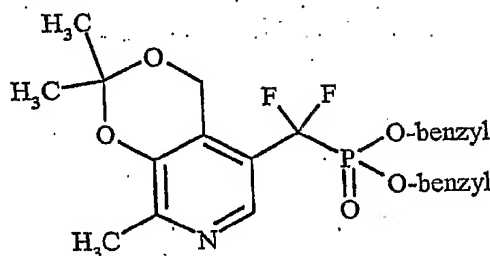
To a solution of dibenzyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylphosphonate (115 mg, 0.253 mmol) in THF (10 mL) was added NaHMDS (1 M, 0.56 mL, 0.56 mmol). The reaction mixture was cooled to -78°C. After 15 minutes, NFSi (237 mg, 0.75 mmol) was added to the reaction mixture. The temperature of the reaction mixture was slowly warmed to -20°C. The solution was diluted with Et₂O, washed with saturated NaHCO₃, water and brine, dried (MgSO₄) and evaporated. The crude product was chromatographed on silica using ethyl acetate:hexanes (2:1) as eluent to give the dibenzyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)difluoromethylphosphonate in good yields.

¹H NMR (CDCl₃) 1.53 (s, 6H), 2.45 (d, 3H), 5.34 (d, 2H), 7.09-7.39 (m, 14H), 8.29 (s, 1H).

³¹P NMR (CDCl₃) -2.15 (t).

¹⁹F NMR (CDCl₃) -105.7 (d).

This structure can be represented by formula:



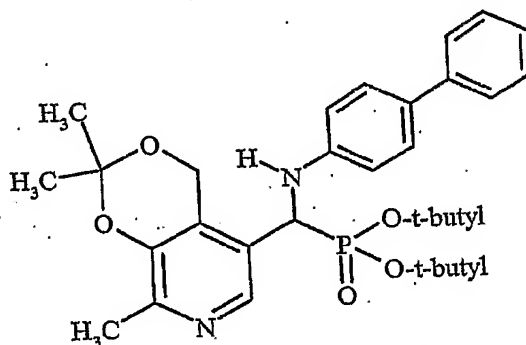
Example 13: Synthesis of di-t-butyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-biphenylamino)methylphosphonate

The ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (424 mg, 2.19 mmol) and 4-aminobiphenyl (360 mg, 2.12 mmol) was refluxed in benzene (20 mL) under nitrogen, using a Dean-Stark trap to remove water, for 15 hours. The crude reaction mixture was evaporated, dissolved in THF (20 mL) and added to a flask containing di-t-butyl phosphite (955 mg, 5.12 mmol) in THF (20 mL) and NaH (270 mg, 57% in oil, 6.41 mmol) and stirred at 0°C for two hours. The solution was diluted with Et₂O, washed with saturated, aqueous NaHCO₃ (40 mL), brine (20 mL), dried (MgSO₄) and evaporated. The crude product was chromatographed on silica gel using hexane:diethyl ether (2:1) to give di-t-butyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-biphenylamino)methylphosphonate in modest yields.

¹H NMR (CDCl₃) 8.40 (1H, d,), 7.50-7.41 (2H, m), 7.40-7.30 (4H, m), 7.28-7.10 (1H, m), 6.54 (1H, d), 5.24 (1H, dd,), 5.07 (1H, dd,), 4.65 (1H, dd,), 4.44 (1H, dd,), 2.40 (3H, d), 1.58 (3H, s), 1.49 (3H, s), 1.43 (9H, s), 1.41 (9H, s).

³¹P NMR (H-decoupled, CDCl₃): 13.1 (s).

This structure can be represented by formula:



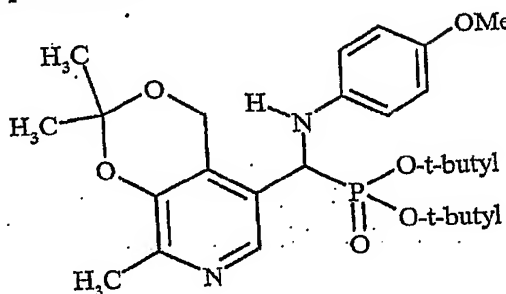
Example 14: Synthesis of di-t-butyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-methoxyphenylamino)methylphosphonate

($\alpha^4,3$ -O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (2.5 g, 12.1 mmol) and 4-aminoanisole (1.41 g, 11.4 mmol) was refluxed in benzene (100 mL) under nitrogen, using a Dean-Stark trap to remove water, for 15 hours. The reaction mixture was evaporated to give 3.02 g of crude imine. The crude imine (370 mg, 1.19 mmol) was dissolved in THF (20 mL) and added to a flask containing di-*t*-butyl phosphite (955 mg, 5.1 mmol) in THF (20 mL) and NaH (208 mg, 57% in oil, 4.94 mmol) and stirred at 0°C for two hours and at room temperature for 24 hours. The solution was diluted with Et₂O, washed with saturated, aqueous NaHCO₃ (40 mL), brine (40 mL), dried (MgSO₄) and evaporated. The crude product was chromatographed on silica gel using hexane:diethyl ether (2:1) to give di-*t*-butyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)(4-methoxyphenylamino)methylphosphonate in modest yields.

¹H NMR (CDCl₃) 8.09 (1H, d), 6.70-6.60 (2H, m), 6.47-6.36 (2H, m), 5.18 (1H, dd), 4.98 (1H, dd), 4.36-4.20 (2H, m), 3.65 (3H, s), 2.35 (3H, s), 1.54 (3H, s), 1.45 (3H, s), 1.39 (9H, s), 1.38 (9H, s).

³¹P NMR (decoupled, CDCl₃): δ 13.5 ppm.

This structure can be represented by formula:



Example 15: Synthesis of di-*t*-butyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-3-azabutylphosphonate

($\alpha^4,3$ -O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylbromide (Imperalli *et al.*, J. Org. Chem., 60, 1891-1894 (1995)) (1.08 g, 4.0 mmol) in anhydrous DMF (20 mL) was treated with sodium azide (260

mg, 4.0 mmol) at room temperature. After one hour stirring at room temperature, the solution was extracted with diethyl ether (5 x 20 mL). The combined extracts were washed with water (10 mL), and brine (10 mL) and dried (MgSO_4). The solvent was evaporated and the crude product was purified by chromatography on silica gel using ethyl ether: hexanes (2:1) as eluent to give the azide as a colorless liquid (552mg, 60%).

^1H NMR (CDCl_3 , TMS) 1.57 (s, 6H), 2.42 (s, 3H), 4.23 (s, 2H), 4.86 (s, 2H), 7.96 (s, 1H).

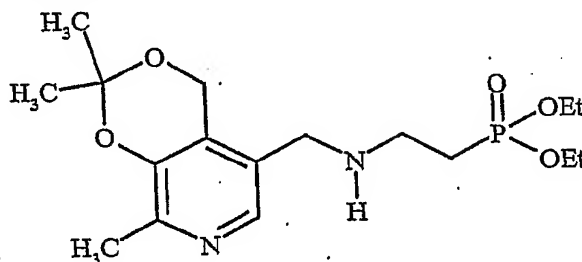
The purified azide (100 mg, 0.4 mmol) was dissolved in 95% ethanol and hydrogenated at 1 atm in presence of Lindlar catalyst (50 mg) for one hour. The catalyst was removed by filtration (Celite), and the solvent removed to give the crude amine. Purification by chromatography on silica gel using CH_2Cl_2 :MeOH (5:1) as eluent gave the product (80 mg, 82%) ^1H NMR (CD_2Cl_2) 1.53 (s, 6H), 2.34 (s, 3H), 3.72 (s, 2H), 4.91 (s, 2H), 5.31 (s, 2H), 7.93 (s, 1H).

The (α^4 ,3-O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylamine, from above, (416 mg, 2 mmol) was heated in saturated, aqueous sodium bicarbonate solution (10 mL) to 95°C, followed by slow addition of diethyl 2-bromoethylphosphonate (0.09 mL, 0.5mmol) and the reaction stirred at 95°C overnight. The solution is evaporated using toluene to codistill the water. The crude product is triturated with ethyl acetate to dissolve the crude organic product. Chromatography on silica gel using methylene chloride:methanol:hexanes (5:1:5) gave 76 mg (41%).

^1H Nmr (CDCl_3 , TMS) 1.27 (t, 6H), 1.51 (s, 6H), 1.91 (t, 2H), 2.35 (s, 3H), 2.85 (t, 2H), 3.62 (s, 2H), 4.03 (m, 4H), 4.91 (s, 2H), 7.88 (s, 1H).

^{31}P NMR (H-decoupled, CDCl_3): 31.00 (s).

This structure can be represented by formula:



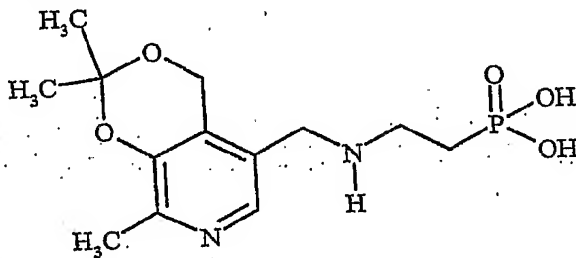
Example 16: Synthesis of (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-3-azabutylphosphonic acid

The product of Example 15, of formula XIX (280 mg, 0.75 mmol) was stirred in a mixture of acetonitrile (6 mL) and trimethylsilylbromide (TMSBr) (574 mg, 3.75 mmol) overnight at room temperature. The solvent was evaporated and the crude product was purified by chromatography on silica gel using dichloromethane:methanol:water (65:35:6) giving 188 mg (91%).

^1H NMR (D_2O) 1.65 (s, 6H), 2.02 (m, 2H), 2.42 (s, 3H), 3.40 (m, 2H), 4.24 (s, 2H), 5.12 (s, 2H), 8.11 (s, 1H).

^{31}P NMR (H-decoupled, D_2O): 18.90 (s).

This structure can be represented by formula:



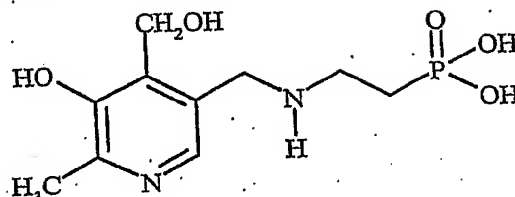
Example 17: Synthesis of (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-3-azabutylphosphonic acid

The product of Example 16, of formula XX (168 mg, 0.53 mmol) was dissolved in acetic acid (80% in water, 10 mL) and heated to 60°C for 5 hours. The solvent was removed by evaporation using toluene to codistill the water. The crude product was purified by chromatography on C-18 reverse phase silica gel using methanol:water (4:1) as eluent to give 57 mg (39%).

^1H NMR (D_2O) 2.05 (m, 2H), 2.52 (s, 3H), 3.38 (m, 2H), 4.42 (s, 2H), 4.96 (s, 2H), 7.87 (s, 1H).

^{31}P NMR (H-decoupled, D_2O): 18.90 (s).

This structure can be represented by formula:



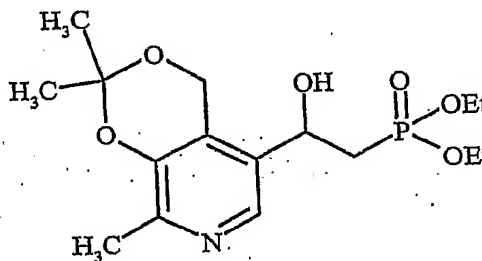
Example 18: Synthesis of diethyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-hydroxyethylphosphonate

To a solution of diethyl methyl phosphite (0.29 mL, 2 mmol) in THF (20 mL) was added BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol), followed by ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (414 mg, 2 mmol) and the reaction mixture stirred at -78°C for two hours. The solution was evaporated, dissolved in dichloromethane (50 mL), washed with saturated, aqueous NaHCO_3 , dried (MgSO_4), evaporated and purified by chromatography on silica gel using ethyl acetate:hexane (1:2) as eluent to give 625 mg (87%).

^1H NMR (CDCl_3 , TMS) 1.33 (m, 6H), 1.54 (s, 6H), 2.20 (m, 2H), 2.38 (s, 3H), 4.12 (m, 4H), 4.94 (s, 2H), 4.94 (s, 2H), 5.04 (t, 1H), 8.02 (s, 1H).

^{31}P NMR (H-decoupled, CDCl_3): 29.03 (s).

This structure can be represented by formula:



Example 19: Synthesis of diethyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-acetoxyethylphosphonate

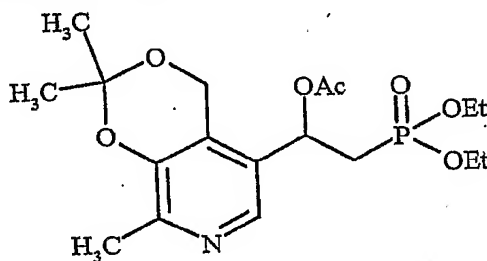
The product of Example 18, of structure XXII (300 mg, 0.84 mmol) was acetylated in pyridine (0.5 mL) and acetic anhydride (0.25 mL) at 0°C for 5 minutes followed by 3 hours at room temperature. The solvent was removed by evaporation using

toluene to codistill the solvents and the crude product was dissolved in dichloromethane (10 mL). This was washed with dilute HCl (10%, 5 mL), then saturated, aqueous NaHCO₃, dried (MgSO₄) and evaporated. Chromatography on silica gel using ethyl acetate:hexane (1:1) gave 258 mg (71%).

¹H NMR(CDCl₃, TMS) 1.21 (m, 6H), 1.54 (s, 6H), 2.03 (s, 3H), 3.97 (m, 4H), 5.07 (dd, 2H), 5.83 (dd, 1H), 8.02 (s, 1H).

³¹P NMR (H-decoupled, CDCl₃): 25.01 (s).

This structure can be represented by formula:



Example 20: Synthesis of diethyl ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-hydroxy-1,1-difluoroethylphosphonate

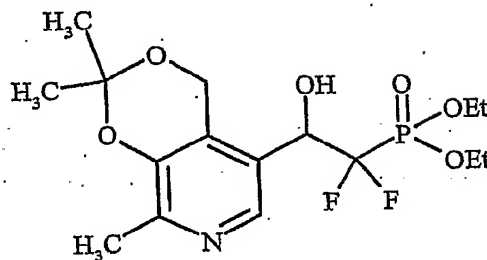
To a solution of lithiumdiisopropylamide (LDA) (2.0 M, 1 mL, 2 mmol) in THF (5 mL) was added BuLi (0.5 M, 0.2 mL, 0.1 mmol). The mixture was cooled to -40°C followed by the addition of diethyl difluoromethyl phosphonate (0.32 mL, 2 mmol) and the reaction mixture stirred at this temperature for 30 minutes. The solution was cooled to -78°C and ($\alpha^4,3$ -O-Isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methanal (Kortynk *et al.*, J. Org. Chem., 29, 574-579 (1964)) (414 mg, 2 mmol) added in THF (2 mL). The solution was allowed to come to room temperature and stirred overnight. The solvent was evaporated, the residue dissolved in dichloromethane (20 mL), washed with saturated, aqueous NaHCO₃, dried (MgSO₄), and evaporated. Purification by chromatography on silica gel using ethyl acetate:hexane (2:1) gave 528 mg (67%)

¹H NMR (CDCl₃, TMS) 1.35 (t, 3H), 1.38 (t, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 2.39 (s, 3H), 4.29 (m, 4H), 4.96 (dd, 3H), 8.09 (s, 1H).

¹⁹F NMR (CDCl₃) -125.99 (ddd), -114.55 (ddd).

³¹P NMR (H-decoupled, CDCl₃): 7.22 (dd).

This structure can be represented by formula:



Example 21: Synthesis of diethyl (α^4 ,3-O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-oxo-1,1-difluoroethylphosphonate

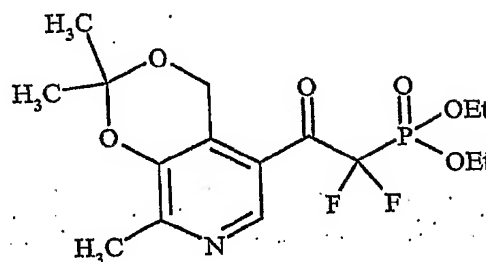
The product of Example 20, of structure XXIV, (420 mg, 1.06 mmol) was dissolved in toluene (50 mL) and MnO_2 (651 mg, 636 mmol) added. The mixture was heated to 50°C and stirred overnight. The solution was cooled, filtered (Celite) and the solvent evaporated to give the crude product. Purification by chromatography on silica gel ethyl acetate (1:2) gave 201 mg (48%).

^1H nmr (CDCl_3 , TMS) 1.39 (q, 6H), 1.56 (d, 6H), 2.51 (s, 3H), 4.34 (m, 4H), 5.08 (s, 2H), 8.88 (s, 1H).

^{19}F NMR (CDCl_3) -109.86 (d).

^{31}P NMR (H-decoupled, CDCl_3): 3.96 (t).

This structure can be represented by formula:



Example 22: Synthesis of diethyl (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-hydroxy-1,1-difluoroethylphosphonate

The product of Example 20, of structure XXIV (489 mg, 1.26 mmol) was dissolved in acetic acid (80% in water, 20 mL) and heated at 80°C for 6 hours. The solvent was removed by evaporation by codistilling with toluene to remove last

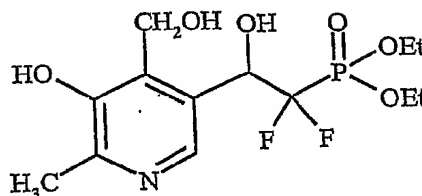
traces of acetic acid. The crude product was purified by chromatography on silica gel using dichloromethane:methanol:hexane (5:1:5) as eluent to give 171 mg (38%).

^1H NMR (CD_3OD) 1.32 (t, 3H), 1.37 (t, 3H), 2.43 (s, 3H), 4.30 (m, 4H), 4.93 (dd, 2H), 5.39 (m, 2H), 8.07 (s, 1H).

^{19}F NMR (CD_3OD) -125.55 (dd), -115.77 (dd).

^{31}P NMR (H-decoupled, MeOD): 7.82 (dd).

This structure can be represented by formula:



Example 23: Synthesis of diethyl (3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-2-oxo-1,1-difluoroethylphosphonate

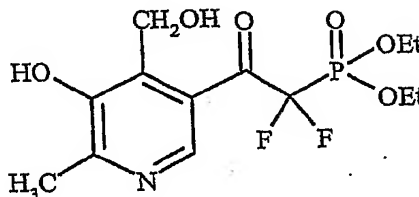
The product of Example 21, of structure XXV (198 mg, 0.51 mmol) was dissolved in acetic acid (80% in water, 20 mL) and heated at 80°C for 6 hours. The solvent was removed by evaporation by codistilling with toluene to remove last traces of acetic acid. The crude product was purified by chromatography on silica gel using dichloromethane:methanol:hexane (5:1:5) as eluent to give 25 mg (14%).

^1H NMR (CDCl_3 , TMS) 1.38 (m, 6H), 2.37 (s, 3H), 4.33 (m, 4H), 4.92 (s, 1H), 7.88 (s, 1H).

^{19}F (CDCl_3) -118.32 (d).

^{31}P NMR (H-decoupled, CDCl_3): 5.90 (t).

This structure can be represented by formula:



Example 24: Synthesis of diethyl ($\alpha^4,3$ -O-isopropylidene-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridylmethyl)malonate

To a solution of diethyl malonate (0.76 mL, 798 mg, 4.98 mmol) in tetrahydrofuran (THF) (5 mL) was added LDA (5 M, 1 mL, 5.0 mmol) and stirred at 0°C for 5 minutes. ($\alpha^4,3$ -O-isopropylidene-3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methylbromide (Imperalli *et al*, J. Org. Chem., 60, 1891-1894 (1995)) (1.36 g, 5.0 mmol) in THF (5 mL) was added. The reaction was stirred for 2 hours at 0°C. The solvent was evaporated and the residue was dissolved in Et₂O. This was washed with water, dried (MgSO₄) and evaporated to give the crude product. Purification of the crude mixture by chromatography on silica gel column using diethyl ether:hexane (1:1) gave the malonate derivative 769 mg (44%).
¹H NMR (CDCl₃, TMS) 1.23 (t, 6H), 1.54 (s, 6H), 2.37 (s, 3H), 3.04 (d, 2H), 3.63 (t, 1H), 4.18 (q, 4H), 4.86 (s, 2H), 7.87 (s, 1H).

Example 25: Treatment of Stress-induced angina with P5P

Patients with a history of exercise induced angina are treated with P5P either before or after the onset of angina. Several measures are used to test the effectiveness of P5P for the treatment of angina including the time to onset of angina, exercise duration, time to 1mm ST depression, and patient pain evaluation. Studies find that onset to angina, time to 1mm ST depression, and patient pain, are all diminished, and exercise duration is increased, in patient groups treated with P5P.

Example 26: Animal models for treatment of stress-induced angina

The canine model of myocardial ischemia, the canine model of exertional dysfunction, and the isolated perfused rat heart model of low flow ischemia, as previously and elsewhere described, is used to determine the effectiveness of P5P, pyridoxal, pyridoxine, and the compounds synthesized in Examples 1-24, to determine effectiveness of these compounds in treatment of angina. Groups treated with P5P, pyridoxal, pyridoxine, and the compounds synthesized in Examples 1-24 show varying symptoms and levels of angina, however, all treatment groups exhibit significantly lower symptoms and levels of angina than untreated or sham treated control animals.

Example 27: Effect of P5P on glucose oxidation rates or cardiac function

Study Design

The goal was to determine if P5P altered glucose oxidation rates or cardiac function in the isolated non-ischemic working rat heart model. This was achieved by subjecting rat hearts to 60 minutes of aerobic perfusion. P5P was added about 5 minutes into the aerobic period and the effects of P5P on glucose metabolism was determined during the aerobic period. Saline control, DCA (dichloroacetic acid) positive control, P5P were tested, with six patients in each group.

Isolated Rat Heart Model

Rat hearts were cannulated for isolated working heart perfusions as described previously (Lopaschuk et al., J Pharmacol Exp Ther. 1993 Jan;264(1):135-44).

In brief, male Sprague-Dawley rats (0.3-0.35 kg) were anesthetized with pentobarbital sodium (60 mg/ kg i. p.). The hearts were quickly excised, the aorta was cannulated, and a retrograde perfusion at 37°C was initiated at a hydrostatic pressure of 60 mm Hg. Hearts were trimmed of excess tissue, and the pulmonary artery and the opening to the left atrium were then cannulated. After 15 min of Langendorff perfusion, hearts were switched to the working mode by clamping the aortic inflow line from the Langendorff reservoir and opening the left atrial inflow line. The perfusate was delivered from an oxygenator into the left atrium at a constant preload pressure of 11 mm Hg. The perfusate was ejected from spontaneously beating hearts into a compliance chamber (containing 1 ml of air) and into the aortic outflow line. The afterload was set at a hydrostatic pressure of 80 mm Hg.

All working hearts were perfused with Krebs-Henseleit solution containing calcium (2.5 mmol/ L), glucose (5.5 mmol/ L), 3% bovine serum albumin (fatty acid free, Sigma), and with palmitate (0.4 mmol/ L). The perfusate was recirculated, and the pH was adjusted to 7.4 by bubbling with a mixture containing 95% O₂ and 5% CO₂. Spontaneously beating hearts were used in all perfusions, heart rate and aortic pressure were measured with a Biopac Systems Inc. blood pressure transducer connected to the aortic outflow line. Cardiac output and aortic flow were measured with Transonic T206 ultrasonic flow probes in the preload and afterload lines,

respectively. Coronary flow was calculated as the difference between cardiac output and aortic flow.

Measurement of Glucose Oxidation:

Glucose oxidation was measured by perfusing the hearts with [^{14}C] glucose. The total myocardial $^3\text{H}_2\text{O}$ production and $^{14}\text{CO}_2$ production were determined at 10-min intervals from the 60-minute aerobic period. Glucose oxidation rates were determined by quantitative measurement of $^{14}\text{CO}_2$ production as described previously. An imbalance between glycolysis and glucose oxidation can explain the detrimental effects of high levels of fatty acids during aerobic reperfusion of ischemic hearts. Lopaschaulk, et al., J Pharmacol Exp Ther. 1993; 264: 135-144.).

Results Glucose Oxidation:

As shown in Figure 1 DCA (positive control) resulted in a significant increase in glucose oxidation rates as compared to control (2422 ± 140 vs. 1580 ± 183 , respectively, $p=0.001$). As well, P5P was able to show a significant increase in glucose oxidation rates when compared to the control (2253 ± 230 vs. 1580 ± 183 , respectively, $p=0.045$).

Therapies that reduce fatty acid oxidation and increase glucose oxidation have been shown to have a clear clinical benefit to patients with either stable angina or unstable angina, without any undesirable hemodynamic effects. (Wolff et al. "Metabolic approaches to the treatment of ischemic heart disease: The clinicians' perspective" Heart Failure Review, 2002, 7:187-203.) Clinical trials with partial fatty acid oxidation inhibitors have showed that the shift in substrate oxidation has antianginal action. A shift from fatty acid oxidation to glucose oxidation leads to a reduced gluconeogenesis and improved economy of cardiac work (Rupp et al. "The use of partial fatty acid oxidation inhibitors for metabolic therapy of angina pectoris and heart failure." Herz 1001 Nov;27(7):621-36.). Clinical trials have also shown that agents, which increase glucose oxidation, either alone or in combination with a Ca^{+2} channel antagonist or a beta-adrenergic receptor antagonist, have demonstrated reduced symptoms of exercise-induced angina (unstable angina). (W.C. Stanley "Partial fatty acid oxidation inhibitors for stable angina." Expert Opinions Investigational drugs, 2002 May; 11(5):615-629.)

Because P5P increases the rate of glucose oxidation in working hearts, it is likely to have a beneficial effect on angina, both stable and unstable.

Example 28: Treatment of stress-induced angina with P5P combination therapies

The experiment of Example 25 is repeated, this time testing combination therapies. Patient groups are as follows: placebo-treated, P5P-treated, propranolol treated, P5P + propranolol treated, verapamil treated, P5P + verapamil treated, ranolazine treated, P5P + ranolazine treated, isosorbide dinitrate treated, P5P + isosorbide dinitrate treated, nicorandil treated, P5P + nicorandil treated. The inventors find that P5P treatment alone improves angina outcomes, confirming the results of Example 25. The inventors find that combination treatments (P5P + propranolol, P5P + verapamil, P5P + ranolazine, P5P + isosorbide dinitrate, P5P + nicorandil) have significantly improved and advantageous angina outcomes when directly compared to treatment with their respective therapeutic angina compounds alone (i.e. propranolol, verapamil, ranolazine, isosorbide dinitrate, and nicorandil, respectively).

Example 29: Treatment of stress-induced angina with pyridoxine combination therapies

The Experiments of Example 28 are repeated, this time using pyridoxine instead of P5P. Patient groups are thus as follows: placebo-treated, pyridoxine treated, propranolol treated, pyridoxine + propranolol treated, verapamil treated, pyridoxine + verapamil treated, ranolazine treated, pyridoxine + ranolazine treated, isosorbide dinitrate treated, pyridoxine + isosorbide dinitrate treated, nicorandil treated, pyridoxine + nicorandil treated. The inventors find that combination treatments (pyridoxine + propranolol, pyridoxine + verapamil, pyridoxine + ranolazine, pyridoxine + isosorbide dinitrate, pyridoxine + nicorandil) have significantly improved and advantageous angina outcomes when directly compared to treatment with their respective therapeutic angina compounds alone (i.e. propranolol, verapamil, ranolazine, isosorbide dinitrate, and nicorandil, respectively).

Example 30: Treatment of stress-induced angina with pyridoxal derivatives in combination therapy

The experiments of Examples 28 and 29 are repeated using the pyridoxal derivatives of Examples 1-26 instead of P5P or pyridoxine. The inventors find that combination treatments have significantly improved and advantageous angina outcomes when directly compared to treatment with their respective therapeutic angina compounds alone.

Example 31: Animal combination therapies

The animal model experiments of Example 26 are repeated, this time with the combination treatment groups as elucidated in Examples 28, 29 and 30. The inventors find that combination treatments have significantly improved and advantageous angina outcomes when directly compared to treatment with their respective therapeutic angina compounds alone.

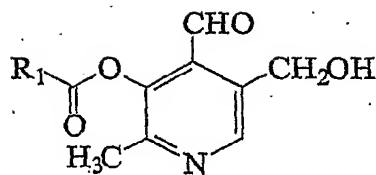
Example 32: Effect of combination therapies on glucose oxidation rates or cardiac function

The experiments of Example 27 are repeated, this time with the combination treatment groups as elucidated in Examples 28, 29 and 30. The inventors find that combination treatments have significantly improved and advantageous angina outcomes when directly compared to treatment with their respective therapeutic angina compounds alone.

Although embodiments of the invention have been described above, it is not limited thereto, and it will be apparent to persons skilled in the art that numerous modifications and variations form part of the present invention insofar as they do not depart from the spirit, nature and scope of the claimed and described invention.

WE CLAIM:

1. A method of treating angina in a mammal comprising administering a therapeutically effective amount of at least one of pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxic acid, or pyridoxamine concurrently with a therapeutically effective amount of a therapeutic angina compound.
2. The method of claim 1, wherein the therapeutic angina compound comprises a therapeutically effective amount of at least one of a calcium channel blocker, a β -adrenergic-blocker, a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or mixtures thereof
3. The method of claim 2, wherein the calcium channel blocker comprises verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.
4. The method of claim 2, wherein the β -adrenergic-blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, or propranolol.
5. The method of claim 2, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.
6. The method of claim 2, wherein the partial fatty acid oxidation inhibitor is ranolazine.
7. The method of claim 2, wherein the potassium channel activator is nicorandil.
8. A method of treating angina in a mammal comprising concurrently administering a therapeutically effective amount of a therapeutic angina compound and a therapeutically effective amount of at least one compound of the formula



wherein

R_1 is alkyl or alkenyl, in which alkyl or alkenyl can be interrupted by nitrogen, oxygen, or sulfur, and can be substituted at the terminal carbon by hydroxy, alkoxy, alkanoyloxy, alkanoyloxyaryl, alkoxyalkanoyl, alkoxycarbonyl, or dialkylcarbamoyloxy;

alkoxy;

dialkylamino;

alkanoyloxy;

alkanoyloxyaryl;

alkoxyalkanoyl;

alkoxycarbonyl;

dialkylcarbamoyloxy;

aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by

alkyl, alkoxy, amino, hydroxy, halo, nitro, or

alkanoyloxy; or

a pharmaceutically acceptable salt thereof.

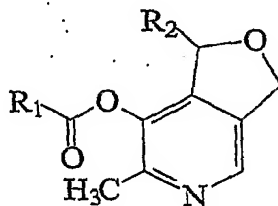
9. The method of claim 8, wherein the therapeutic angina compound comprises a therapeutically effective amount of at least one of a calcium channel blocker, a β -adrenergic-blocker, a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or a mixture thereof

10. The method of claim 9, wherein the calcium channel blocker comprises verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

11. The method of claim 9, wherein the β -adrenergic-blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, or propranolol.

12. The method of claim 9, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.
13. The method of claim 9, wherein the partial fatty acid oxidation inhibitor is ranolazine.
14. The method of claim 9, wherein the potassium channel activator is nicorandil.
15. The method of claim 8, wherein said R₁ is phenyl or naphthyl in which phenyl or naphthyl is unsubstituted or substituted by one or more groups of C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, hydroxy, halo, nitro, or C₁₋₄ alkanoyloxy.
16. The method of claim 8, wherein said R₁ is (2-acetoxy-2-methyl)propanyl, dimethylamino, or 1-ethanoyloxy-1-methylethyl.
17. The method of claim 8, wherein said R₁ is *tert*-butyl.
18. The method of claim 8, wherein said R₁ is methoxy or ethoxy.
19. The method of claim 8, wherein said R₁ is toluyl, naphthyl, phenyl, acetylphenyl, or 1-ethanoyloxyphenyl.
20. The method of claim 8, wherein said R₁ is acetylsalicyl, dimethylamino, or 2,2-dimethylethyl.
21. The method of claim 8, wherein said compound is 2-methyl-3-toluoyloxy-4-formyl-5-hydroxymethylpyridine.
22. The method of claim 8, wherein said compound is 2-methyl-3- β -naphthoyloxy-4-formyl-5-hydroxymethylpyridine.

23. A method of treating angina in a mammal comprising concurrently administering a therapeutically effective amount of a therapeutic angina compound and a therapeutically effective amount of at least one compound of the formula



wherein

R_1 is alkyl or alkenyl, in which alkyl or alkenyl can be interrupted by nitrogen, oxygen, or sulfur, and can be substituted at the terminal carbon by hydroxy, alkoxy, alkanoyloxy, alkanoyloxyaryl, alkoxyalkanoyl, alkoxycarbonyl, or dialkylcarbamoyloxy;

alkoxy;

dialkylamino;

alkanoyloxy;

alkanoyloxyaryl;

alkoxyalkanoyl;

alkoxycarbonyl;

dialkylcarbamoyloxy;

aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by

alkyl, alkoxy, amino, hydroxy, halo, nitro, or

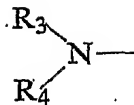
alkanoyloxy; and

R_2 is a secondary amino group; or

a pharmaceutically acceptable salt thereof.

24. The method of claim 23, wherein the therapeutic angina compound comprises a therapeutically effective amount of at least one of a calcium channel blocker, a β -adrenergic-blocker, a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or a mixture thereof

25. The method of claim 24, wherein the calcium channel blocker comprises verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.
26. The method of claim 24, wherein the β -adrenergic-blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, or propranolol.
27. The method of claim 24, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.
28. The method of claim 24, wherein the partial fatty acid oxidation inhibitor is ranolazine.
29. The method of claim 24, wherein the potassium channel activator is nicorandil.
30. The method of claim 23, wherein said R_1 is phenyl or naphthyl in which phenyl or naphthyl is unsubstituted or substituted by one or more groups of C_{1-4} alkyl, C_{1-4} alkoxy, amino, hydroxy, halo, nitro, or C_{1-4} alkanoyloxy.
31. The method of claim 23, wherein said R_1 is (2-acetoxy-2-methyl)propanyl, dimethylamino, or 1-ethanoyloxy-1-methylethyl.
32. The method of claim 23, wherein said wherein R_1 is *tert*-butyl.
33. The method of claim 23, wherein said wherein R_1 is methoxy or ethoxy.
34. The method of claim 23, wherein said R_1 is toluylyl, naphthyl, phenyl, or 1-ethanoyloxyphenyl.
35. The method of claim 23, wherein said R_1 is dimethylamino, acetylsalicyl, or 2,2-dimethylethyl.
36. The method of claim 23, wherein said R_2 is a group of the formula



wherein R_3 and R_4 are each independently alkyl or when taken together form a ring with the nitrogen atom and which ring may optionally be interrupted by a nitrogen or oxygen atom.

37. The method of claim 23, wherein said R_2 is piperidino.

38. The method of claim 23, wherein said R_2 is morpholino or piperazino.

39. The method of claim 23, wherein said compound is 1-morpholino-1,3-dihydro-7-(*p*-toluoyloxy)-6-methylfuro(3,4-*c*)pyridine.

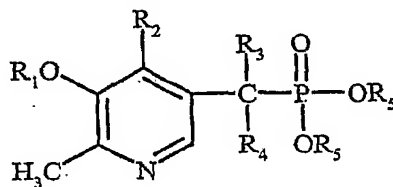
40. The method of claim 23, wherein said compound is 1-morpholino-1,3-dihydro-7-(β -naphthoyloxy)-6-methylfuro(3,4-*c*)pyridine.

41. The method of claim 23, wherein said compound is 1-morpholino-1,3-dihydro-7-pivaloyloxy-6-methylfuro(3,4-*c*)pyridine.

42. The method of claim 23, wherein said compound is 1-morpholino-1,3-dihydro-7-(dimethylcarbamoyloxy)-6-methylfuro(3,4-*c*)pyridine.

43. The method of claim 23, wherein said compound is 1-morpholino-1,3-dihydro-7-acetylsalicyloxy-6-methylfuro(3,4-*c*)pyridine.

44. A method of treating angina in a mammal comprising concurrently administering a therapeutically effective amount of a therapeutic angina compound and a therapeutically effective amount of at least one compound of the formula



wherein

R₁ is hydrogen or alkyl;

R₂ is -CHO, -CH₂OH, -CH₃, -CO₂R₆ in which R₆ is hydrogen, alkyl, or aryl;
or

R₂ is -CH₂O-alkyl- in which alkyl is covalently bonded to the oxygen at the
3-position instead of R₁;

R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino or
arylamino; or

R₃ and R₄ are halo; and

R₅ is hydrogen, alkyl, aryl, aralkyl, or -CO₂R₇ in which R₇ is
hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable salt thereof.

45. The method of claim 44, wherein the therapeutic angina compound comprises a therapeutically effective amount of at least one of a calcium channel blocker, a β -adrenergic-blocker, a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or a mixture thereof.

46. The method of claim 45, wherein the calcium channel blocker comprises verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

47. The method of claim 45, wherein the β -adrenergic-blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, or propanolol.

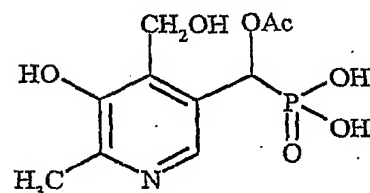
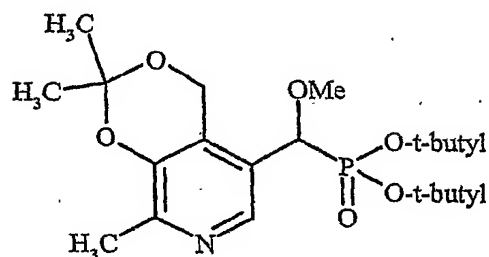
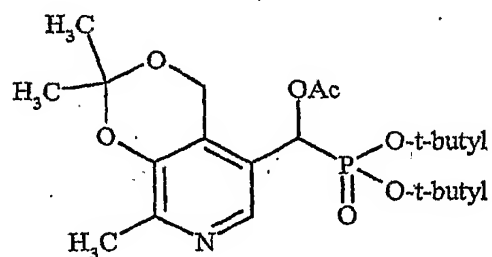
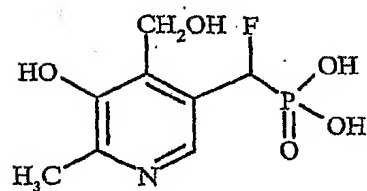
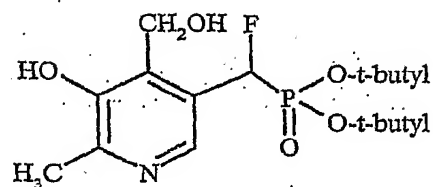
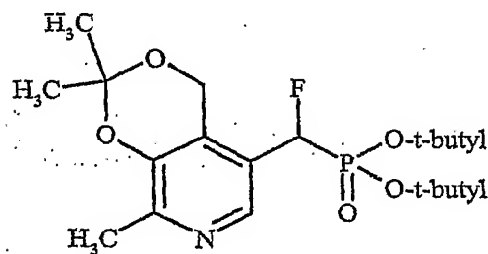
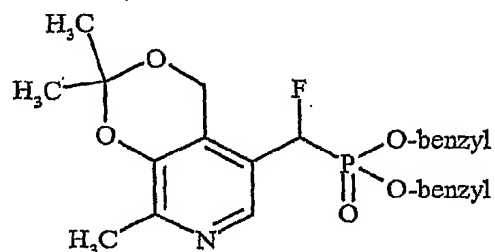
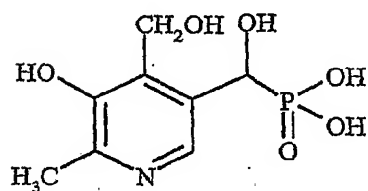
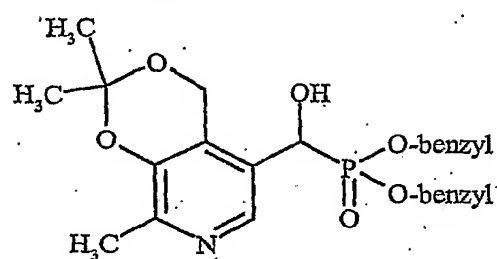
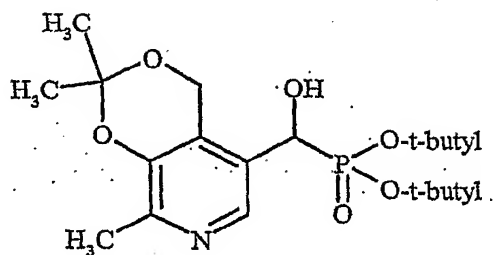
48. The method of claim 45, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

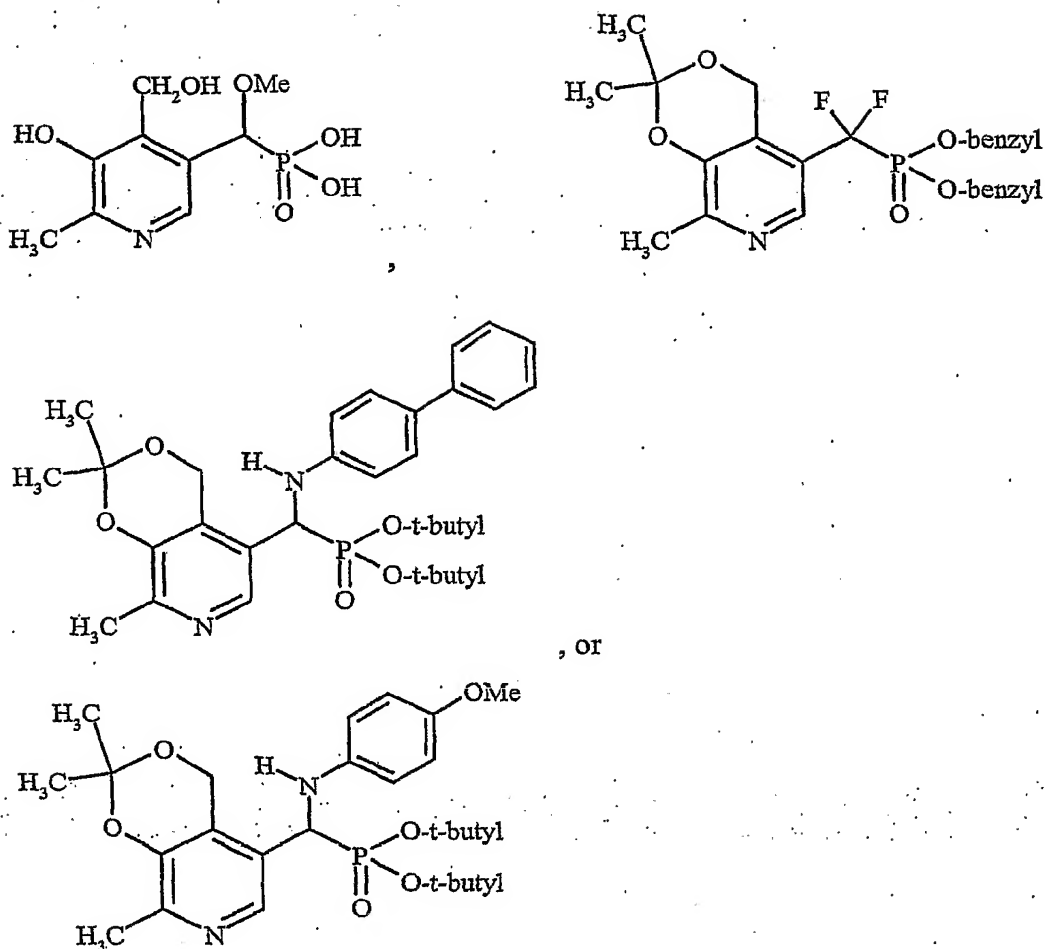
49. The method of claim 45, wherein the partial fatty acid oxidation inhibitor is ranolazine.

50. The method of claim 45, wherein the potassium channel activator is nicorandil.

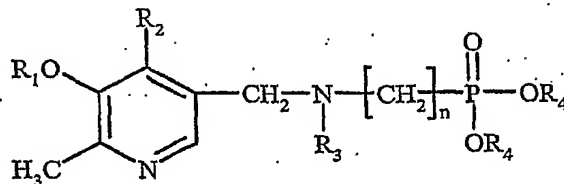
51. The method of claim 44, wherein said R_1 is hydrogen.
52. The method of claim 44, wherein said R_2 is $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 .
53. The method of claim 44, wherein said R_3 is hydrogen and R_4 is F, MeO- , or $\text{CH}_3\text{C(O)O-}$.
54. The method of claim 44, wherein said R_3 and R_4 are F.
55. The method of claim 44, wherein said R_5 is alkyl or aralkyl.
56. The method of claim 44, wherein said R_5 is t-butyl or benzyl.

57. The method of claim 44, wherein said compound is





58. A method of treating angina in a mammal comprising concurrently administering a therapeutically effective amount of a therapeutic angina compound and a therapeutically effective amount of at least one compound of the formula



wherein

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$ or $-\text{CO}_2\text{R}_5$ in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is $-\text{CH}_2\text{-O-alkyl-}$ (in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1);

R_3 is hydrogen, alkyl, aryl, or aralkyl;

R_4 is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2R_6$ in which R_6 is hydrogen, alkyl, aryl, or aralkyl; and

n is 1 to 6;

or a pharmaceutically acceptable salt thereof.

59. The method of claim 58, wherein the therapeutic angina compound comprises a therapeutically effective amount of at least one of a calcium channel blocker, a β -adrenergic-blocker, a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or a mixture thereof

60. The method of claim 59, wherein the calcium channel blocker comprises verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

61. The method of claim 59, wherein the β -adrenergic-blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, or propranolol.

62. The method of claim 59, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

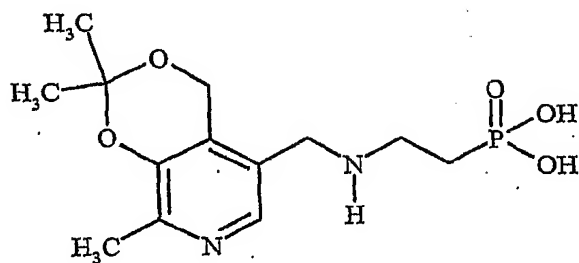
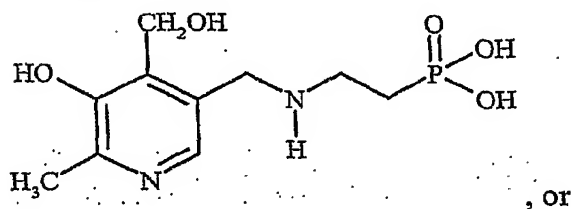
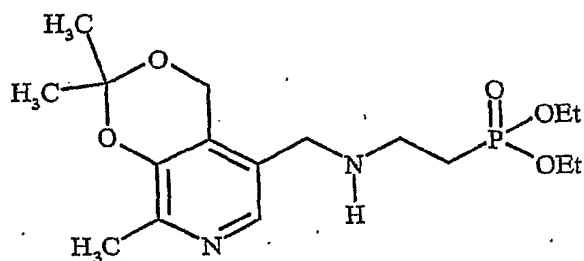
63. The method of claim 59, wherein the partial fatty acid oxidation inhibitor is ranolazine.

64. The method of claim 59, wherein the potassium channel activator is nicorandil.

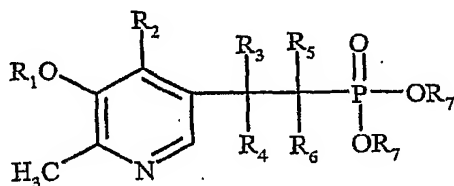
65. The method of claim 58, wherein said R_1 is hydrogen.

66. The method of claim 58, wherein said R_2 is $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{-O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 .

67. The method of claim 58, wherein said R_3 is hydrogen.
68. The method of claim 58, wherein said R_4 is alkyl or H.
69. The method of claim 58, wherein said R_4 is ethyl.
70. The method of claim 58, wherein said compound is



71. A method of treating angina in a mammal comprising concurrently administering a therapeutically effective amount of a therapeutic angina compound and a therapeutically effective amount of at least one compound of the formula



in which

R₁ is hydrogen or alkyl;

R₂ is -CHO, -CH₂OH, -CH₃ or -CO₂R₈ in which R₈ is hydrogen, alkyl, or aryl; or

R₂ is -CH₂-O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁;

R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy or alkanoyloxy; or

R₃ and R₄ can be taken together to form =O;

R₅ and R₆ are hydrogen; or

R₅ and R₆ are halo; and

R₇ is hydrogen, alkyl, aryl, aralkyl, or -CO₂R₈ in which R₈ is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable salt thereof.

72. The method of claim 71, wherein the therapeutic angina compound comprises a therapeutically effective amount of at least one of a calcium channel blocker, a β -adrenergic-blocker, a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, or a mixture thereof.

73. The method of claim 72, wherein the calcium channel blocker comprises verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

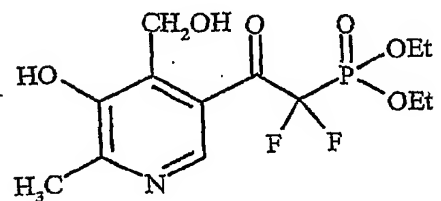
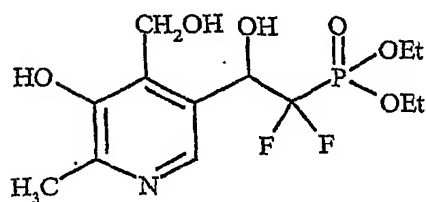
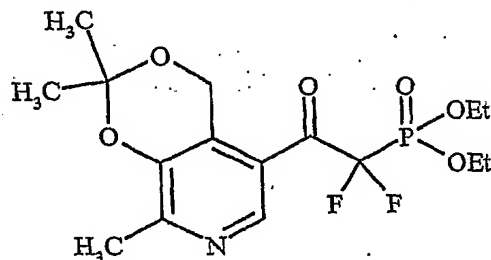
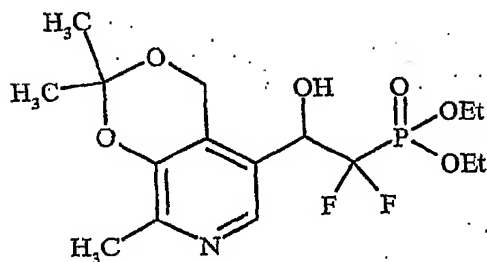
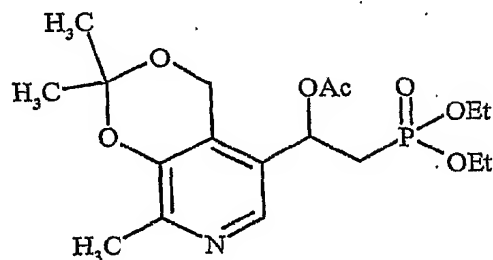
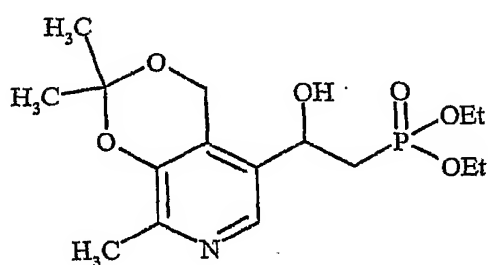
74. The method of claim 72, wherein the β -adrenergic-blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, or propranolol.

75. The method of claim 72, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

76. The method of claim 72, wherein the partial fatty acid oxidation inhibitor is ranolazine.

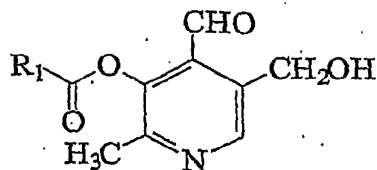
77. The method of claim 72, wherein the potassium channel activator is nicorandil.

78. The method of claim 71, wherein said R_1 is hydrogen.
79. The method of claim 71, wherein said R_2 is $-\text{CH}_2\text{O}$ or $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 .
80. The method of claim 71, wherein said R_4 is $-\text{OH}$ or $\text{CH}_3\text{C}(\text{O})\text{O-}$.
81. The method of claim 71, wherein said R_3 and R_4 taken together form $=\text{O}$.
82. The method of claim 71, wherein said R_5 and R_6 are F.
83. The method of claim 71, wherein said R_7 is alkyl.
84. The method of claim 71, wherein said R_7 is ethyl.
85. The method of claim 71, wherein said compound is



, or

86. A composition comprising a therapeutically effective amount of at least one of pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxic acid, or pyridoxamine and a therapeutically effective amount of a therapeutic angina compound.
87. A composition comprising a therapeutically effective amount of at least one of pyridoxal-5'-phosphate, pyridoxal, pyridoxine, pyridoxic acid, or pyridoxamine and a therapeutically effective amount of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic-blocker, or a mixture thereof.
88. The composition of claim 87, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.
89. The composition of claim 87, wherein the partial fatty acid oxidation inhibitor is ranolazine.
90. The composition of claim 87, wherein the potassium channel activator is nicorandil.
91. The composition of claim 87 wherein the calcium channel blocker is verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.
92. The composition of claim 87 wherein the β -adrenergic blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol or propranolol.
93. A composition comprising a therapeutically effective amount of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic-blocker, or a mixture thereof and a therapeutically effective amount of at least one compound of the formula



wherein

R_1 is alkyl or alkenyl, in which alkyl or alkenyl can be interrupted by nitrogen, oxygen, or sulfur, and can be substituted at the terminal carbon by hydroxy, alkoxy, alkanoyloxy, alkanoyloxyaryl, alkoxyalkanoyl, alkoxycarbonyl, or dialkylcarbamoyloxy;

alkoxy;

dialkylamino;

alkanoyloxy;

alkanoyloxyaryl;

alkoxyalkanoyl;

alkoxycarbonyl;

dialkylcarbamoyloxy;

aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by

alkyl, alkoxy, amino, hydroxy, halo, nitro, or

alkanoyloxy; or

a pharmaceutically acceptable salt thereof.

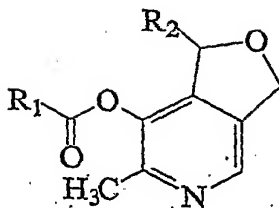
94. The composition of claim 93, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

95. The composition of claim 93, wherein the partial fatty acid oxidation inhibitor is ranolazine.

96. The composition of claim 93, wherein the potassium channel activator is nicorandil.

97. The composition of claim 93 wherein the calcium channel blocker is verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

98. The composition of claim 93 wherein the β -adrenergic blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol or propranolol.
99. The composition of claim 93, wherein said R_1 is phenyl or naphthyl in which phenyl or naphthyl is unsubstituted or substituted by one or more groups of C_{1-4} alkyl, C_{1-4} alkoxy, amino, hydroxy, halo, nitro, or C_{1-4} alkanoyloxy.
100. The composition of claim 93, wherein said R_1 is (2-acetoxy-2-methyl)propyl, dimethylamino, or 1-ethanoyloxy-1-methylethyl.
101. The composition of claim 93, wherein said R_1 is *tert*-butyl.
102. The composition of claim 93, wherein said R_1 is methoxy or ethoxy.
103. The composition of claim 93, wherein said R_1 is tolyl, naphthyl, phenyl, acetylphenyl, or 1-ethanoyloxyphenyl.
104. The composition of claim 93, wherein said R_1 is acetylsalicyl, dimethylamino, or 2,2-dimethylethyl.
105. The composition of claim 93, wherein said compound is 2-methyl-3-toluoxy-4-formyl-5-hydroxymethylpyridine.
106. The composition of claim 93, wherein said compound is 2-methyl-3- β -naphthoyloxy-4-formyl-5-hydroxymethylpyridine.
107. A composition comprising a therapeutically effective amount of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic blocker, or a mixture thereof and a therapeutically effective amount of at least one compound of the formula



wherein

R₁ is alkyl or alkenyl, in which alkyl or alkenyl can be interrupted by nitrogen, oxygen, or sulfur, and can be substituted at the terminal carbon by hydroxy, alkoxy, alkanoyloxy, alkanoyloxyaryl, alkoxyalkanoyl, alkoxycarbonyl, or dialkylcarbamoxyloxy;

alkoxy;

dialkylamino;

alkanoyloxy;

alkanoyloxyaryl;

alkoxyalkanoyl;

alkoxycarbonyl;

dialkylcarbamoxyloxy;

aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy; and

R₂ is a secondary amino group; or

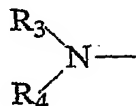
a pharmaceutically acceptable salt thereof.

108. The composition of claim 107, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

109. The composition of claim 107, wherein the partial fatty acid oxidation inhibitor is ranolazine.

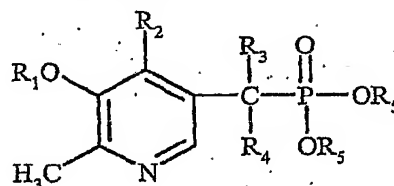
110. The composition of claim 107, wherein the potassium channel activator is nicorandil.

111. The composition of claim 107 wherein the calcium channel blocker is verapamil, diltiazem, nifeipine, felodipine, amlodipine, or nisoldipine.
112. The composition of claim 107 wherein the β -adrenergic blocker is acebutolol, atenolol, labetalolol, metoprolol, nadolol, pindolol or propanolol.
113. The composition of claim 107, wherein said R_1 is phenyl or naphthyl in which phenyl or naphthyl is unsubstituted or substituted by one or more groups of C_{1-4} alkyl, C_{1-4} alkoxy, amino, hydroxy, halo, nitro, or C_{1-4} alkanoyloxy.
114. The composition of claim 107, wherein said R_1 is (2-acetoxy-2-methyl)propanyl, dimethylamino, or 1-ethanoyloxy-1-methylethyl.
115. The composition of claim 107, wherein said wherein R_1 is *tert*-butyl.
116. The composition of claim 107, wherein said wherein R_1 is methoxy or ethoxy.
117. The composition of claim 107, wherein said R_1 is toluyyl, naphthyl, phenyl, or 1-ethanoyloxyphenyl.
118. The composition of claim 107, wherein said R_1 is dimethylamino, acetylsalicyl, or 2,2-dimethylethyl.
119. The composition of claim 107, wherein said R_2 is a group of the formula



wherein R_3 and R_4 are each independently alkyl or when taken together form a ring with the nitrogen atom and which ring may optionally be interrupted by a nitrogen or oxygen atom.

120. The composition of claim 107, wherein said R_2 is piperidino.
121. The composition of claim 107, wherein said R_2 is morpholino or piperazino.
122. The composition of claim 107, wherein said compound is 1-morpholino-1,3-dihydro-7-(*p*-toluoyloxy)-6-methylfuro(3,4-*c*)pyridine.
123. The composition of claim 107, wherein said compound is 1-morpholino-1,3-dihydro-7-(β -naphthoyloxy)-6-methylfuro(3,4-*c*)pyridine.
124. The composition of claim 107, wherein said compound is 1-morpholino-1,3-dihydro-7-pivaloyloxy-6-methylfuro(3,4-*c*)pyridine.
125. The composition of claim 107, wherein said compound is 1-morpholino-1,3-dihydro-7-(dimethylcarbamoyloxy)-6-methylfuro(3,4-*c*)pyridine.
126. The composition of claim 107, wherein said compound is 1-morpholino-1,3-dihydro-7-acetylsalicyloxy-6-methylfuro(3,4-*c*)pyridine.
127. A composition comprising a therapeutically effective amount of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic blocker, or a mixture thereof and a therapeutically effective amount of at least one compound of the formula



wherein

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$, $-\text{CO}_2\text{R}_6$ in which R_6 is hydrogen, alkyl, or aryl;

or

R₂ is -CH₂-O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁;

R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino or arylamino; or

R₃ and R₄ are halo; and

R₅ is hydrogen, alkyl, aryl, aralkyl, or -CO₂R₇ in which R₇ is hydrogen, alkyl, aryl, or aralkyl;

or a pharmaceutically acceptable salt thereof.

128. The composition of claim 127, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

129. The composition of claim 127, wherein the partial fatty acid oxidation inhibitor is ranolazine.

130. The composition of claim 127, wherein the potassium channel activator is nicorandil.

131. The composition of claim 127 wherein the calcium channel blocker is verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

132. The composition of claim 127 wherein the β -adrenergic blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol or propranolol.

133. The composition of claim 127, wherein said R₁ is hydrogen.

134. The composition of claim 127, wherein said R₂ is -CH₂OH, or -CH₂-O-alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁.

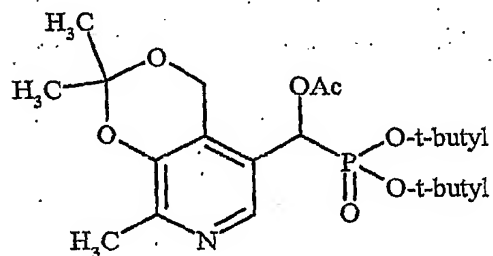
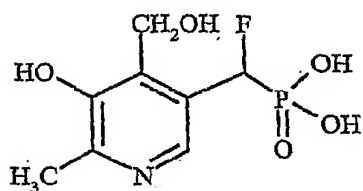
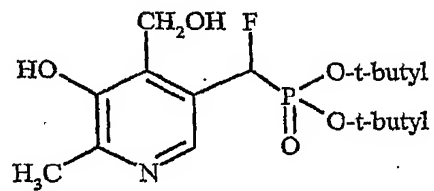
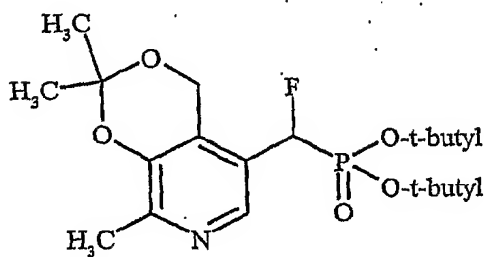
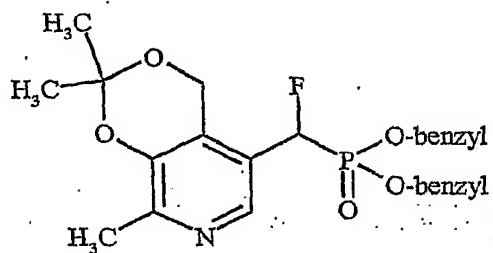
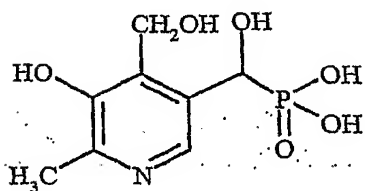
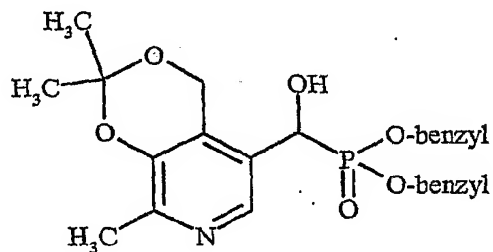
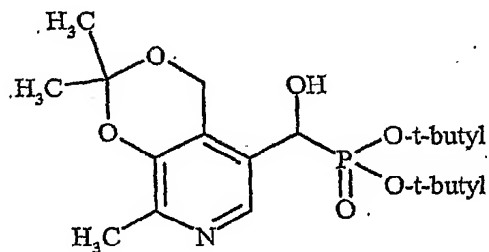
135. The composition of claim 127, wherein said R₃ is hydrogen and R₄ is F, MeO-, or CH₃C(O)O-.

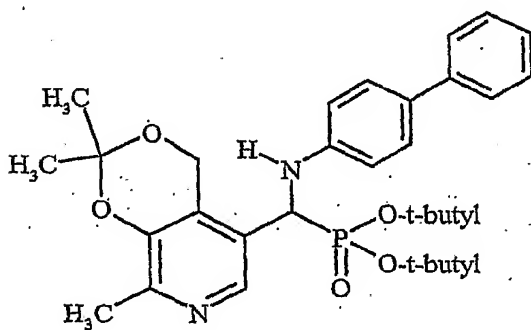
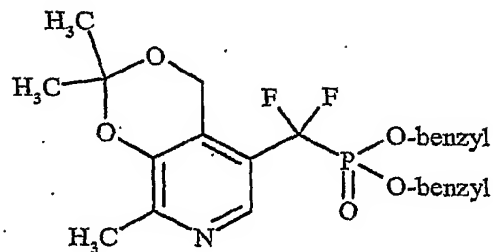
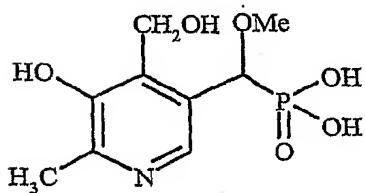
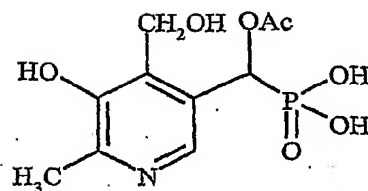
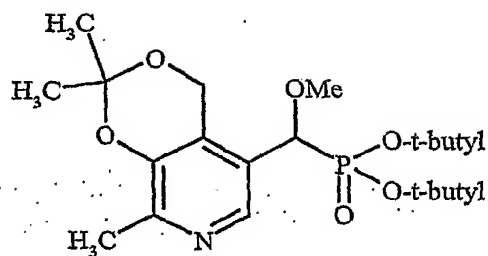
136. The composition of claim 127, wherein said R₃ and R₄ are F.

137. The composition of claim 127, wherein said R_5 is alkyl or aralkyl.

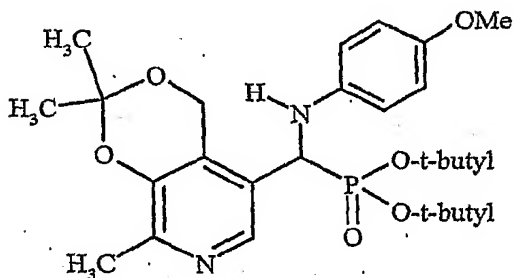
138. The composition of claim 127, wherein said R_5 is t-butyl or benzyl.

139. The composition of claim 127, wherein said compound is

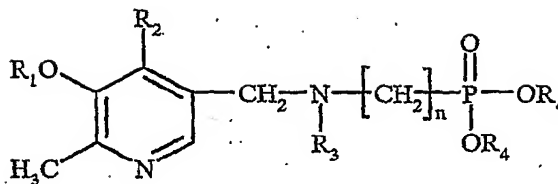




, or



140. A composition comprising a therapeutically effective amount of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic blocker, or a mixture thereof and a therapeutically effective amount of at least one compound of the formula



wherein

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$ or $-\text{CO}_2R_5$ in which R_5 is hydrogen, alkyl, or aryl; or

R_2 is $-\text{CH}_2\text{O-alkyl-}$ (in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1);

R_3 is hydrogen, alkyl, aryl, or aralkyl;

R_4 is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2R_6$ in which R_6 is hydrogen, alkyl, aryl, or aralkyl; and

n is 1 to 6;

or a pharmaceutically acceptable salt thereof.

141. The composition of claim 140, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

142. The composition of claim 140, wherein the partial fatty acid oxidation inhibitor is ranolazine.

143. The composition of claim 140, wherein the potassium channel activator is nicorandil.

144. The composition of claim 140 wherein the calcium channel blocker is verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

145. The composition of claim 140 wherein the β -adrenergic blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol or propanolol.

146. The composition of claim 140, wherein said R_1 is hydrogen.

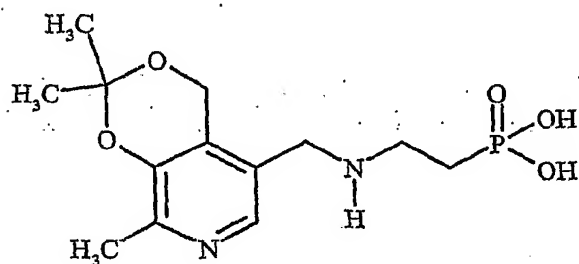
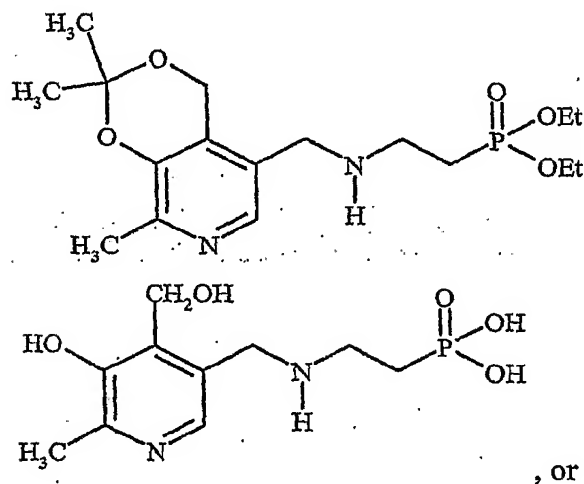
147. The composition of claim 140, wherein said R_2 is $-\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 .

148. The composition of claim 140, wherein said R_3 is hydrogen.

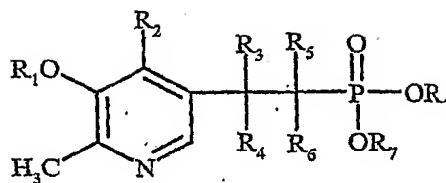
149. The composition of claim 140, wherein said R_4 is alkyl or H.

150. The composition of claim 140, wherein said R_4 is ethyl.

151. The composition of claim 140, wherein said compound is



152. A composition comprising a therapeutically effective amount of a nitrate, a partial fatty acid oxidation inhibitor, a potassium channel activator, a calcium channel blocker, a β -adrenergic blocker, or a mixture thereof and a therapeutically effective amount of at least one compound of the formula



in which

R_1 is hydrogen or alkyl;

R_2 is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$ or $-\text{CO}_2\text{R}_8$ in which R_8 is hydrogen, alkyl, or aryl; or

R_2 is $-\text{CH}_2\text{O-alkyl-}$ in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 ;

R_3 is hydrogen and R_4 is hydroxy, halo, alkoxy or alkanoyloxy; or

R_3 and R_4 can be taken together to form $=\text{O}$;

R_5 and R_6 are hydrogen; or

R_5 and R_6 are halo; and

R_7 is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2\text{R}_8$ in which R_8 is hydrogen, alkyl, aryl, or aralkyl; or a pharmaceutically acceptable salt thereof.

153. The composition of claim 152, wherein the nitrate comprises nitroglycerine, isosorbide dinitrate, or isosorbide mononitrate.

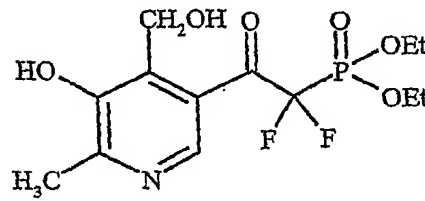
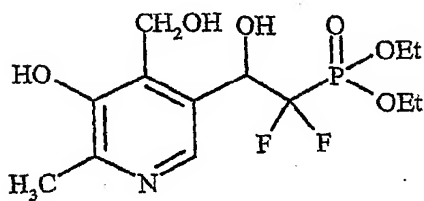
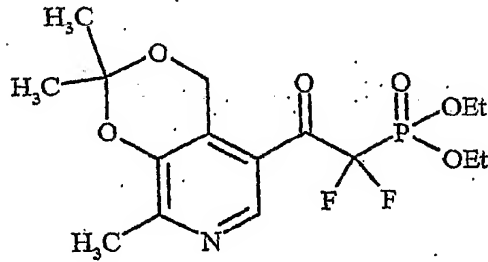
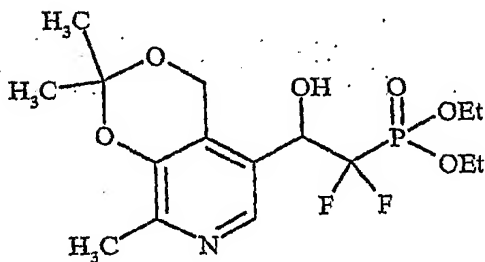
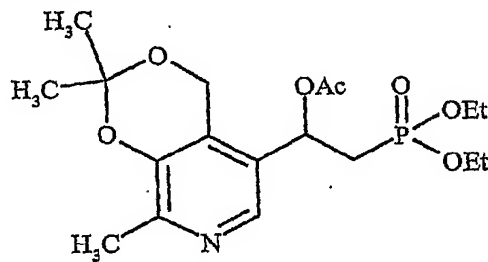
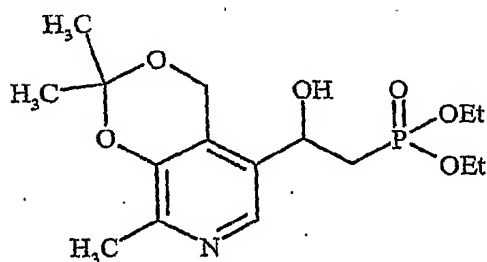
154. The composition of claim 152, wherein the partial fatty acid oxidation inhibitor is ranolazine.

155. The composition of claim 152, wherein the potassium channel activator is nicorandil.

156. The composition of claim 152 wherein the calcium channel blocker is verapamil, diltiazem, nifedipine, felodipine, amlodipine, or nisoldipine.

157. The composition of claim 152 wherein the β -adrenergic blocker is acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol or propranolol.

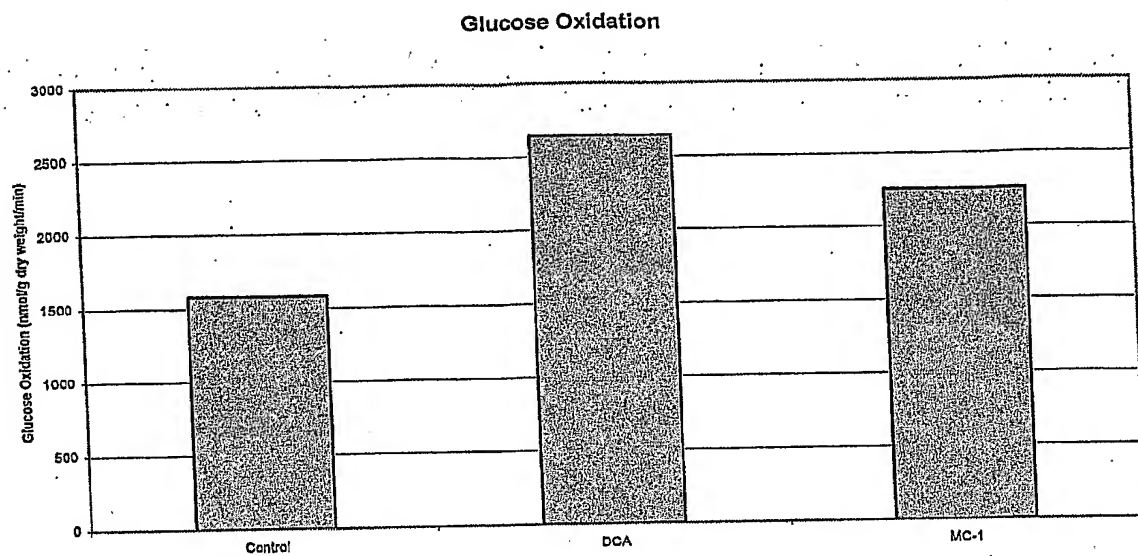
158. The composition of claim 152, wherein said R_1 is hydrogen.
159. The composition of claim 152, wherein said R_2 is $-CH_2O$ or $-CH_2O$ -alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of R_1 .
160. The composition of claim 152, wherein said R_4 is $-OH$ or $CH_3C(O)O-$.
161. The composition of claim 152, wherein said R_3 and R_4 taken together form $=O$.
162. The composition of claim 152, wherein said R_5 and R_6 are F.
163. The composition of claim 152, wherein said R_7 is alkyl.
164. The composition of claim 152, wherein said R_7 is ethyl.
165. The composition of claim 152, wherein said compound is



, or

166. The use of a composition of any one of claims 86 to 165 for the treatment of angina.

167. The use of a composition of any one of claims 86 to 165 for preparation of a pharmaceutical for the treatment of angina.

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001470

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7): A61K 31/675, A61P 9/10, A61K 31/4415, A61K 31/44, A61K 31/34, A61K 31/496, A61K 31/4406, A61K 31/277, A61K 31/138

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/675, A61P 9/10, A61K 31/4415, A61K 31/44, A61K 31/34, A61K 31/496, A61K 31/4406, A61K 31/227, A61K 31/138

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Delphion, Scopus, PubMed, Internet, Espacenet

Key Words: angina, glucose oxidation, fatty acid oxidation inhibitor, ischemia, pyridoxal, pyridox*, phosphonate*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/13900 (SETHI, R et al.) 01-03-2001 abstract, pages 13-14	1-4, 8-11, 15-26, 30-43, 86-88, 91-94, 97-108, 111-126, 166-167
Y	PHAM, V et al. 'Design and synthesis of novel pyridoxine-5'-phosphonates as potential antiischemic agents.' J. Med. Chem. 14-08-2003, Vol 46(17) p3680-7 abstract and pages 3681-3682	1-4, 44-47, 51-57, 127, 131-139, 166-167
Y	STANLEY, W.C. 'Partial fatty acid oxidation inhibitors for stable angina' Expert Opinion on Investigative Drugs, 05-2002, Vol 11(5), Pages 615-629 (Cited in the application) Pages 616, 617, 622, 623, 625.	1-4, 44-47, 51-57, 127, 131-139, 166-167
L	'Stedman's Medical Dictionary' 1961, Waverly Press Inc. Baltimore, Md., page 101, Defn. angina.	1-167
A	RUPP, H et al. 'The use of partial fatty acid oxidation inhibitors for metabolic therapy of angina pectoris and heart failure', Herz, 11-2002, Vol 27(7), page 621-636 entire document.	1-167

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 25 November 2005 (25-11-2005)	Date of mailing of the international search report 28 November 2005 (28-11-2005)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer James Martyn (819) 953-0761

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001470

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 1 - 85

because they relate to subject matter not required to be searched by this Authority, namely :

The subject matter of claims 1 - 85 relate to methods of medical treatment of the human or animal body (Rule 39.1(iv) PCT). For the assessment of these claims with respect to their industrial applicability (Article 33(4) PCT), no unified criteria exists in the PCT. The patentability of the subject matter defined by these claims may depend on the formulation of the claims in the different member states. Certain national offices accept claims worded as *methods of medical treatment*, while other offices accept claims worded as *use claims* and would recognize the industrial applicability for the subject matter of medical use claims.

2. ☐ Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001470

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DYCK, J.R.B. et al. 'Malonyl CoA control of fatty acid oxidation in the ischemic heart', J. Mol. Cell Cardiol., 09-2002, Vol 34(9), pages 1099-1109 entire document	1-167
A	LOPASCHUK, G.D. et al. 'Glucose metabolism in the ischemic heart', Circulation, 1997, Vol 95, page 313-315 entire document	1-167

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001470

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO0113900	01-03-2001	AU6814400 A	19-03-2001
		CA2383252 A1	01-03-2001
		EP1210117 A2	05-06-2002
		JP2003507418T T	25-02-2003
		US6677356 B1	13-01-2004
		US2004033989 A1	19-02-2004
		US2004033990 A1	19-02-2004
		US2004033991 A1	19-02-2004
		US2004033992 A1	19-02-2004
		US2004033993 A1	19-02-2004
US2004038945 A1	26-02-2004		
